THE CANADIAN MEDICAL ASSOCIATION

LE JOURNAL DE

L'ASSOCIATION MÉDICALE CANADIENNE

APRIL 23, 1960 • VOL. 82, NO. 17

THE BOUNDLESS REALM OF ANÆSTHESIOLOGY*

HAROLD R. GRIFFITH, M.D., F.R.C.P.[C.], Hon.F.F.A.R.C.S.,† *Montreal*

I FEEL very highly honoured indeed to be invited to deliver the first Dr. Harry Shields Lecture in Anæsthesia. The University of Toronto and the Toronto General Hospital have become world-recognized centres for the teaching of anæsthesiology—and Harry Shields, more than anyone else, has been the originator, the planner, the director of this teaching program. Dr. Shields has been associated with the Toronto General Hospital ever since he started in anæsthesia (except for the years during the First World War when he was one of the few qualified anæsthetists in the Canadian Army Overseas) and during all these years, in addition to his teaching responsibilities, he has taken a major part in the administraton of the anæsthesia service of the hospital; he has personally cared for many thousands of patients; and he has made friends of all those he has served—patients, medical colleagues, students, and others. A great outpouring of sympathy, understanding and friendship has been perhaps his most lasting contribution to the development of anæsthesia in Canada.

As a title for this lecture I have chosen "The Boundless Realm of Anæsthesiology" in order to emphasize not only the way in which the interest and responsibility of the anæsthetist have expanded, but also the bewildering and apparently limitless way in which the field is still expanding. I shall try not to succumb to the temptation of reminiscence, but I cannot help but recall that when I started to administer anæsthetics 40 years ago, the attitude of the medical profession generally was that this was a rather boring technical procedure which could be carried out by students, interns, or broken-down doctors who had failed at the really important aspects of the practice of medicine. It was a way to put in time while one was learning to be a surgeon, and I must confess that my first interest was prompted by the opportunity to earn a few $5.00 fees while I was working my way through medical school. The hospital in which I gave my first anæsthetics (and where I have remained ever since) was typical of that day in that there was no regular anæsthetist, no oxygen, no suction, gas machines, airways or endotracheal tubes, and the complete anæsthesia equipment consisted of a bottle of chloroform, a few cans of ether, and a gauze-covered wire mask.

Fortunately for the progress of anæsthesiology in Canada there were even then a few men who had caught the vision of better service to the patient in this field. Samuel Johnston, Charles Robson, William Easson Brown and Harry Shields in Toronto; Wesley Bourne and Charles Larocque in Montreal, and William Webster in Winnipeg were far ahead of the times in their work in anæsthesia. For this reason some Canadian hospitals, and notably the Toronto General Hospital, have for many years been in a leading position in both the technique and the teaching of anæsthesia. Anæsthesia in Canada has always been considered a part of the practice of medicine, requiring the services of physicians, so that we were never involved to any serious extent in the controversy which still goes on in the United States and in some other countries regarding the administration of anæsthetics by nurses and technicians.

A dawning realization that the role of the anæsthetist could be more than that of a technician came relatively early in Canada. Back in 1920, when the original Canadian Society of Anæsthetists was being formed, the founders chose as its motto the Greek words "Katheudontas parateroumen" (we watch closely those who sleep). It was then a revolutionary concept that the anæsthetist's responsibility rested primarily in watching the condition of the patient rather than the rate of ether drops from the bottle, or the expression on the surgeon's face. That motto has continued right up to the present as the guiding principle of our Canadian Society, although today it might be amplified into "We watch closely those who are going to sleep, those who sleep, and those who have slept." This expansion of the anæsthetist's realm of interest has come about gradually as, over the years, more and more thoughtful, intelligent doctors have begun to realize the comprehensive nature of medical problems posed by surgery and concomi-

*This address was delivered at the University of Toronto on October 30, 1959, as the first annual Dr. Harry Shields Lecture in Anæsthesia.

†Emeritus Professor of Anæsthesia, McGill University.

tant anæsthesia, and the imperative need, in the patient's interest, for finding a solution to most of these problems.

So, I propose now briefly to relate how anæsthesiology today, in contrast to 40 years ago, has become the most comprehensive of all specialties. The anæsthetist, in addition to his technical skill, must have the wisdom of a physician, and an appreciation of the problems of surgeons and obstetricians. He must be familiar with the extraordinary conditions involved in all the surgical specialties. He must be a clinical pharmacologist, because he deals with all kinds of drugs; a biochemist and physiologist of sorts because he is responsible for the maintenance of vital function under widely varying conditions: and he must be a practical psychologist because he deals with patients at times of peculiar strain and stress. He should also be humble in relations with his professional colleagues, gentle, courteous and kind to all with whom he works in the hospital. In spite of these formidable requirements, the anæsthetists of Canada have grown into a veritable host. In fact, we are now the largest group of certified specialists outside the ranks of internal medicine and general surgery. There are nearly 700 certified anæsthetists in Canada, and more than 1000 members of the Canadian Anæsthetists' Society.

How has this transformation from the old days come about? Probably the most important factor has been more and better teaching. When I started we picked up what we know just by ourselves on a trial-and-error basis. My early years were not even an apprenticeship, because there was no one to be apprenticed to. I did have the good fortune, however, to work in the same city with Wesley Bourne, who was an inspiration to me to do good work, as he has been to so many young anæsthetists. As the years went by, the challenge of better anæsthesia began to interest more young doctors, and many who are now leaders in our specialty got into practice after a year or two of residency in Montreal or Toronto, or in some English or American hospital. At the University of Wisconsin, Dr. Ralph Waters established the first really comprehensive program for the training of anæsthetists. He was able to demonstrate how there could be an effective integration of clinical teaching on anæsthesiology with specialized instruction in the basic sciences, and he provided the inspiring leadership which stimulated the interest of pharmacologists, physiologists, physicians and surgeons, as well as a very distinguished group of students. Waters at Madison, and to some extent John Lundy at the Mayo Clinic, were the gardeners who planted the seeds from which have grown the present departments of anæsthesiology in most of the American medical schools.

In Canada, even before Waters' time, Easson Brown at Toronto, and Wesley Bourne at McGill, were demonstrating, through long hours of personal work in the laboratories, that anæsthesia and pharmacology are inseparable partners and that some knowledge of biochemistry is a fundamental requirement for an anæsthetist. Brown, in co-operation with Professors Velyan Henderson and George Lucas, discovered the anæsthetic properties of ethylene, cyclopropane, and ethyl-N-propyl ether; but co-ordination between clinicians and laboratory workers had not then developed sufficiently at the University of Toronto to get these important discoveries into the hospital operating rooms. At McGill, Wesley Bourne worked in the department of pharmacology for many years, in his so-called "leisure time", and was one of the first of modern anæsthetists to investigate basic physiological problems concerned with the administration of anæsthetics, and the effects of anæsthetic agents on the vital metabolic processes. Dr. Bourne became so concerned with the biochemical basis of anæsthesia that many years later when he published a volume of his essays he gave it the intriguing title "Mysterious Waters to Guard," borrowing the words of Shelley when he says—

> "O stream!
> Whose source is inaccessibly profound,
> Whither do thy mysterious waters tend?
> Thou imagest my life."

The human body is indeed made up of mysterious waters, and it is the anæsthetist's duty to guard these waters through some of the most turbulent moments of life.

So new concepts for the anæsthetist gradually became apparent. The leaders of the rapidly developing specialty found themselves concerned with three parallel problems—

1. The development of new drugs and techniques of administration that would keep pace with and enhance the progress of surgery.
2. A better understanding of the basic sciences in relation to anæsthesia—an imperative need if new drugs and techniques were to be used safely.
3. Better provisions for the teaching of anæsthesiology.

All these phases of the development of anæsthesiology have progressed in a simultaneous and parallel fashion. It is difficult, and perhaps futile, to speculate as to which is the most important.

I. DRUGS AND TECHNIQUES

Work in regard to drugs and apparatus has been exciting, and good fun. When one sees the formidable and expensive anæsthesia machines of today, one must admit that this is at least a change from the old "rag and bottle" days. Some of these changes have been more significant than others. In my opinion the two most important are the development and popularization of *endotracheal tubes* with their emphasis on clear airways; and secondly and more recently, the great extension of interest in *adequate pulmonary ventilation.*

Endotracheal tubes are now such an indispensable part of the anæsthetist's equipment that it is

hard to believe that a few years ago they were almost unknown. The first paper I ever read at a medical meeting was in 1928 in Boston, entitled "Intratracheal Ethylene Anæsthesia." It was received by most of the audience with great scepticism because 90% of the anæsthetists of the United States at that time had never intubated a patient. Fortunately for me, Dr. Ralph Waters happened to be in the audience, and recognized a new young advocate of the doctrine which he and Guedel had been preaching—the supreme importance of a clear airway. Dr. Waters introduced himself, and this led to a friendship which over the years has meant much to me. In Canada, for years before that, we had been administering ether by intratracheal insufflation, and Hargraves in Toronto, and Stewart in Montreal, had developed large tubes for nitrous oxide. A great variety of tubes were tried, and now we have all come to using some variation of the endotracheal tubes designed by Magill of London, to which has been added Guedel-Waters' inflatable cuff. Today, the endotracheal tube is indeed a "life line" for the patient under anæsthesia.

So far as anæsthetic apparatus is concerned, I still believe there is virtue in simplicity, and the most complex machine is not always the best. In some operating rooms the surgeon and patient are squeezed into a small corner to make room for the apparatus which counts and records innumerable body functions as well as delivering the anæsthetic. Up to the present the ultimate in automation is probably the machine developed by Bickford, Faulconer and their associates at the Mayo Clinic, which automatically maintains the level of anæsthesia by turning valves on or off in accordance with the electroencephalographic pattern of the patient. This is fine for experiment and investigation, but in my opinion it is utter nonsense to try to make such a device applicable to regular clinical anæsthesia. Variations of electroencephalographic curves are only one of the infinite number of variable factors in a human being, and I cannot conceive of any machine which could instantly take into account all of these factors more effectively than the human intelligence of an anæsthetist. Perhaps such a machine might be devised, but it would certainly be a complicated and expensive way of carrying out a procedure which we can now do simply and quickly by using our own brains. So I continue to be an advocate of simple gas machines with dependable easily-read flow meters; accurate vapourizers; efficient CO_2 absorbers; and not too many tricky valves or by-passes.

Sir Robert Macintosh of Oxford, who has, perhaps, done more than anyone else to spread the gospel of good anæsthesia throughout the world, is a consistent advocate of simplicity in techniques and equipment. I visited him one year when he had just returned from a trip to Indonesia, where he had been demonstrating anæsthesia in a country of seventy million people and three anæsthesiologists. His essential equipment consisted of an ether vapourizer, hand-operated bellows, and some endotracheal tubes. He expressed the unorthodox view that "no life is ever saved by oxygen that could not have been saved by air. Why use oxygen from a tank when we have God's oxygen all about us in 20% concentration?" Even if one does not entirely agree with this doctrine, one must admit that there is much to be said in favour of simplicity.

The fundamental equipment necessary for administration, therefore, consists of a laryngoscope, endotracheal tubes, vapourizer or flow meters, and some kind of ventilator. We realize now, much more than we did twenty-five years ago, that carbon dioxide elimination is just as vital as oxygenation. With present-day drugs, when one respiratory depressant is often piled on top of another, we cannot just depend on the patient's doing his own pulmonary ventilation (as in the days of open-drop ether). Dr. Shields was one of the first to point out the importance of assisted or controlled ventilation as a concomitant of modern anæsthesia. Then, for some years we believed that the so-called "educated hand" of the anæsthetist squeezing the breathing bag was more efficient than any mechanical device. Now, I am not so sure. Studies with infra-red CO_2 analyzers set up under conditions of clinical anæsthesia have proved to us that a good mechanical ventilator is a most efficient device for removing alveolar CO_2, particularly in long operations. There are now a number of such ventilators available and in my opinion one must be included as essential equipment of a modern anæsthesiology department. So much, then, for equipment.

The development of new drugs has been even more revolutionary. It is unnecessary for me to enumerate all the drugs we now have on our shelves in addition to the old originals—ether and chloroform, and nitrous oxide. Many of the anæsthetic agents which have appeared have been hailed as the ideal, their use boomed into popularity and then they faded away or settled into a particular niche of special usefulness. We have seen this happen with ethyl chloride, ethylene, tribromoethanol, sodium amobarbital, hexobarbital, thiopental, divinylether, cyclopropane, cocaine, procaine, nupercaine, xylocaine, halothane and countless others. It seems to me that the criterion as to the speed of acceptance of a new drug is whether the drug does meet a real need, and the criterion as to whether the new drug finds a permanent and important place in clinical medicine is whether this drug meets this need more effectively and with greater safety than similar drugs presently available. In all branches of medicine new drugs are now being introduced in bewildering profusion, and many are simply variations of previously accepted drugs, whose only title to fame is that they are more expensive or have shown slightly different side effects in laboratory animals. I need not elaborate this point because every doctor knows it to be true, in spite of our admiration and friendship for the pharmaceutical manufacturers. To turn to the other side of the

picture, I would like to speak of two drugs in which I have had much interest over many years, and which met the criteria for final and wide acceptance. I refer to cyclopropane and curare.

When the anæsthetic properties of cyclopropane were announced here at the University of Toronto in 1929, Dr. Ralph Waters was one of the few forward-looking anæsthesiologists who immediately visualized the possibilities of the new agent. Here at last was a potent anæsthetic, non-toxic in its metabolic effects, permitting high oxygenation and with all the advantages of controllability which go with an inhalation gas. In other words, here was something to meet a long-felt need. The clinical trials which followed confirmed Professor Waters' hopes, and the era of cyclopropane anæsthesia soon dawned. After a visit to Madison, I had the privilege of administering the first clinical cyclopropane anæsthesia in Canada in October 1933. I could spend a long time expounding the advantages of cyclopropane and explaining why after twenty-six years we still use it more often than any other agent, but will resist the temptation. I just cite cyclopropane as an example of a drug which met a need.

One could say the same thing about curare. The need for better muscle relaxation during anæsthesia was recognized by every anæsthetist who ever sat shivering under the glowering eyes and blistering tongue of the surgeons of the "good old days". It happens that, in 1942, I had the good fortune, or temerity, or foolhardiness, to introduce into clinical anæsthesia a new preparation of the fabulous drug curare, which certainly met that need. This has had a surprising effect on my subsequent professional career and led to many new adventures, but I think really that I have been given much more credit than I deserve. All that my colleague, Enid Johnson, and I did was to carry out a suggestion which was made to us, and which others had turned down.

Dr. Lewis Wright, of New York, told me of the work being done by Bennett in Nebraska with a new preparation of curare used for the purpose of softening convulsions in shock therapy for psychiatric patients. He thought this "Intocostrin" might be used safely for muscle relaxation in anæsthesia, but everyone had laughed at him. I reasoned that if this curare preparation did not kill the psychiatric patients it should be even safer in the operating room, because anæsthetists are dealing every day with respiratory paralysis. So on January 23, 1942, at the Homœopathic Hospital of Montreal (now the Queen Elizabeth Hospital) we gave the curare to a young man undergoing appendicectomy with cyclopropane anæsthesia. The drug worked, there was no untoward effect, and we used it cautiously in other cases. We published our first report in "Anesthesiology" (August 1942), and others took up the work.

The use of curare in anæsthesia soon spread around the world, and led in some years to the introduction of other muscle relaxing agents; and indirectly to the ganglionic blocking drugs, to the phenothiazine derivatives and all the tranquillizers which now flood the drug stores. I shall leave this subject here with the comment that in spite of doubts and questionings in high scientific circles, and in spite of a period of opposition by some well-known anæsthesiologists, curare or similar drugs are now being used every day in almost every operating room in the world. This seems to me to be a prime example of the rapid acceptance of a new drug when it safely meets a real need.

II. PROBLEMS OF PHYSIOLOGY AND BIOCHEMISTRY

During recent years all medical men have become more interested in how the body works, and how to maintain normal function in the vital organs. When I was a medical student the functions of the liver, for instance, were even more of a mystery than they are today. We did not even know enough to realize how little we did know. We knew nothing of fluid and electrolyte balance, or the problems of blood transfusion, and little about vitamins. No clinician was concerned with enzymology or the intricacies of cellular metabolism, and endocrinology was almost a blank. Today there are many of these problems about which we still do not know much, but we know that they do concern the clinician. There is no branch of clinical medicine where there is greater need for an understanding of basic sciences than there is in anæsthesiology, and no one has a better opportunity to study basic problems than the anæsthetist. The anæsthetist must deal with a patient who is handicapped not only by disease, but also by drugs and by the assault of the surgeon. Take, for example, the problems of respiration. Physicians who have made a specialty of this field have learned a great deal about such things as the metabolic effects of emphysema, of depressed and obstructed respiration, of chronic cough, etc. The anæsthetist must know not only all about these matters, but also about the effects and the management of complete respiratory paralysis produced often by his own drugs, and in a patient existing temporarily in a completely artificial atmosphere.

As a result of thinking along such lines, and because of the advent of new drugs, new apparatus and new operations, our concept of how to conduct anæsthesia has undergone a gradual transformation. We used to feel that anæsthetic sleep should closely simulate natural sleep. Now we realize that this is impossible, partly because we do not yet know enough basically about natural sleep to be able to simulate it, but mainly because we must in anæsthesia do things to the patient which produce conditions far removed from natural sleep and in which the basic metabolic responses are very different indeed. In 1951, Dr. John Gillies, of Edinburgh, coined the term "physiological trespass" to describe some of the things which the anæsthetist is now purposely and almost nonchalantly doing to the patient, in order to obtain conditions which make

modern surgery feasible and safe. Gillies' trespasses included hypotension, apnœa, and muscle paralysis. This sort of trespass every anæsthetist accepts as the inevitable concomitant of certain surgical operations. Besides these trespasses there are others due to posture, sudden hæmorrhage, and surgical trauma: so the anæsthetist today has abandoned any attempt to waft the patient into natural sleep and bends all his efforts to protecting vital functions under these grossly abnormal conditions, and to restoring the patient to comfortable normality after the period of trespass is over. We watch the patient more closely than ever, but now we try to exercise our art in evaluating pulse and blood pressure changes, the electrocardiographic pattern, blood and biochemical requirements, oxygenation, carbon dioxide elimination, peripheral circulation, and many other matters. I believe the usual rapid and fairly comfortable recovery of patients from operations which were in the old days either formidable adventures or unheard of, has justified this expansion of the interest of the anæsthetist. It has, however, brought problems regarding the supply of such omniscient people. Simultaneously with the development of new drugs and methods, and of new conceptions, there has been a revolutionary development in the education of the anæsthetist.

III. Educational Developments

I have often been asked where I received my training in anæsthesiology. My answer must be the same as that of many others of the senior men in this room—I just picked up what I could, however I could, as I engaged in general practice. Until fifteen years ago there was no formal or organized specialist anæsthesia training in Canada. Those who were interested either taught themselves or served an apprenticeship in one of the larger hospitals. During the war we had the opportunity in Montreal to organize intensive three- or four-month courses for medical officers in all three services. This led to the recognition by McGill that there was need for better teaching facilities, and in 1946, the Department of Anæsthesia was established within the Faculty of Medicine, with Dr. Wesley Bourne the first Professor and Chairman. There was soon a parallel development at the University of Toronto under the leadership of Dr. Harry Shields, and since that time these two great Canadian medical schools, in friendly rivalry but close co-operation, have built up teaching programs which have set a standard widely copied throughout Canada and in other countries. The curriculum of these postgraduate specialty training courses includes clinical residency at selected hospitals on a rotation basis, and also basic science lectures, seminars, colloquia and various reading and discussion group meetings. The program for the current year's work at McGill lists 195 of these sessions for students of anæsthesia. We think our type of training is perhaps the most comprehensive of any medical school, but development along the same general lines has been widespread throughout the English-speaking countries, and is now becoming established in Europe and South America. There are now at least eleven journals of anæsthesiology published regularly in various countries. With all these opportunities for education there is now no need for a serious student to remain in ignorance. The demand for qualified anæsthetists is still far ahead of the supply in every country, for anæsthetists are now being recognized as a very useful kind of doctor.

The comprehensiveness of our interests and of our technical skills has resulted in increasing our responsibilities in the modern hospital care of patients. We are called upon to do many things which seem fantastically far removed from the traditional anæsthetist's role. We may supervise oxygen therapy, recovery rooms, blood banks and emergency departments. We are called for difficult intravenous injections, for lumbar punctures, for tracheal intubations and bronchial suction therapy, for the control of convulsions and barbiturate poisonings, for diagnostic and therapeutic nerve blocks, for emergency bronchoscopies and tracheostomies—in other words, we are just handy people to have around. We anæsthetists welcome this recognition of our duty as physicians, although we sometimes wonder just where the limit should be to such an expansion of our realm. There is, however, one field in which I am sure the anæsthetist is better qualified than other consultants who are often asked for, that is in the preoperative assessment of the risk of operation and the preparation of the patient. The cardiologist understands hearts, but he does not know much about the techniques and stresses of either surgery or anæsthesiology, and not much about the behaviour of hearts under the influence of anæsthetic drugs. All of these are things the anæsthetist must deal with every day, and I believe the anæsthetist should be the one to decide the kind of anæsthetic to be used and the way in which the patient is to be prepared for it. The same is true to some extent of immediate postoperative care. Not many surgeons are alert to the problems of postoperative respiration, to the causes of postoperative restlessness, to the differentiation between delirium of drugs and that produced by toxic states. It is often to the patient's advantage if the anæsthetist assumes responsibility in the recovery room, and sometimes for much longer periods. The question of responsibility for postoperative care should be a matter for consultation and co-operation between anæsthetist and surgeon. Indeed, it is a matter which I view with some alarm. For years we have fought for the recognition of our knowledge; and now many surgeons would like to let us go on looking after their patients for days postoperatively, and let us treat all the complications which are not directly related to the area of operation. This is a tendency shown by some general surgeons, as well as by obstetricians,

Canad. M. A. J.
April 23, 1960, vol. 82

ophthalmologists, otolaryngologists and other specialists. The anæsthetists are conveniently available day or night, and in my hospital at least, many times in recent years they have been in constant attendance for a week or more conducting treatment and making decisions which I believe should really be the responsibility of the surgeon.

We may have to get round to treating problem cases by committee. In many hospitals, plans are being made to establish intensive care areas for the concentrated medical and nursing care of the very sick patient. At the new Queen Elizabeth Hospital of Montreal, now under construction, we will have 38 beds (15% of our total capacity) allotted to this type of intensive care. Anæsthetists do not want to assume all the responsibility for seeing that things run smoothly in this area, but I can foresee that much will be expected of us. At present we have a committee studying the problem—an internist, a surgeon, an obstetrician, and some other specialists, as well as a general practitioner, and with an anæsthetist as chairman.

Because anæsthetists have infiltrated so deeply into fundamental medical and hospital problems, I believe we are in a position to enunciate certain principles which may help to get other specialists back into more effective thinking regarding the over-all care of the patient. These principles I shall enumerate briefly:

1. The patient is a whole individual who cannot be divided up into compartments. I know this is a truism, but from my observation I am amazed at how often this seems to be forgotten by those who are concerned with an eye, or an ear, or a stomach or a uterus. Even the radiologist in his enthusiasm for diagnosis often forgets that the patient he is prodding, or purging, or standing on his head is a sick individual.

2. A knowledge of and an application of basic sciences is essential to the good practice of medicine and surgery. Physiology, pharmacology, biochemistry and pathology are not subjects we learn during our training years and then put away forever in the dusty cupboards of our brains. I am distressed when I see young surgeons who have obtained their F.R.C.S. act as if this basic science knowledge was acquired only to pass examinations and need not be used in practice. The older surgeons depended on intuition and experience to steer their patients through the hazards of operations. Today, surgeons need just as much wisdom and common sense, but they also have at hand the tools of biochemistry, of fluid and electrolyte estimation, and many other tests which can be lifesaving if they will take the trouble to sit down and think intelligently in regard to the needs of each patient individually. Anæsthetists are aware of these tools and know how to use them, but we do not think surgeons should just hand over the patient to us.

3. Drugs can be dangerous. This is another truism, but we are in an era of an extravagant use of drugs. New drugs are coming upon us every day, far too rapidly for any doctor to become familiar with the proper use of all of them. Many drugs have so-called side effects which, in our enthusiasm for specific therapy, we often forget or ignore. Anæsthetists know that adrenaline in the eye affects the heart; that pontocaine used for a bronchogram may be so rapidly absorbed as to cause convulsions; that antibiotics, especially when introduced intraperitoneally, may have profound and disastrous effects on respiration; and that sedatives may mask anoxia. We plead with our medical and surgical colleagues to take a second look and give a second thought before they burden a patient who is already handicapped by disease with an unnecessary load of drugs. I often think of the wisdom of the old homœopathic principles on which I was reared—that the *proper* dose of any drug is the *smallest* dose which will effect a cure, and that one drug at a time is better than a mixture.

4. The next item of advice from anæsthetists is a reminder that technical skill in an emergency may be lifesaving. This advice is directed perhaps particularly to the medical specialists. We think every doctor should be able to pass an endotracheal tube, or at least be able to clear an airway and re-establish respiration. The carrying out of lumbar punctures, thoracentesis, intravenous administrations and cut-downs, sternal punctures and other simple procedures is shunned by hospital physicians. It is so easy to write an order to have such things performed by an intern or resident, or to send for the anæsthetic department. We do not object to being called in to do these things, particularly in an emergency, but we think that it would be good for some of the practising physicians to continue to be skilled at such procedures themselves.

5. The next reminder from the wisdom of the anæsthesiologist is that there were never two people born exactly alike. Even in such simple laboratory animals as mice or guinea pigs there are individual differences and the reactions to drugs or to stress show wide variations. How much more important are these sometimes unpredictable and inexplicable variations of human patients. Anæsthetists have learned to prepare their patients individually, but also to be prepared for the unexpected. We believe that there is no excuse in modern hospitals for preoperative or postoperative "routine orders". The very term makes me shudder. No surgeon should ever think that he is too busy to give orders personally for his patient as an individual.

6. Finally, our patients, who are to be treated as individuals, should be treated with sympathy as well as with science. It is so easy to be kind to people if we just make it a habit, and it means so much to the patient. Nothing does more harm to the medical profession than a reputation for being hard-boiled, indifferent, unapproachable, or hard to find. These qualities are not typical, but they are sufficiently prevalent to make us take stock of ourselves. The anæsthetist knows how the smooth-

ness of preoperative care, the operation itself, and the period of recovery can be influenced by such intangibles as mental distress, worry, fear, and anger on the one hand, and by calmness, courage and faith on the other. The quality of kindness is more important than any drug or technique. Let us all – anæsthetist, surgeon, physician, and nurse – cultivate a spirit of kindness as our most important duty.

I have said enough, perhaps too much, about all the virtues of the anæsthetist. I have tried to show how the realm of anæsthesiology is indeed becoming boundless. We really do not want it to be boundless, if only the rest of the hospital team will reoccupy some of the fields over which we willy-nilly have recently spread ourselves. So much remains to be learned in our own narrower and traditional sphere. There is need for basic laboratory research and careful clinical study into hundreds of problems which still confront us.

RÉSUMÉ

L'anesthésiologie a parcouru beaucoup de chemin depuis l'époque, dont l'auteur se souvient très bien, où le matériel d'anesthésie de tout hôpital se limitait à un masque ouaté, une bouteille de chloroforme et une bouteille d'éther. En effet cette spécialité est maintenant devenue une de celles qui exigent le plus de connaissances puisque l'anesthésiste doit posséder la sagesse du médecin et pour une bonne part l'expérience clinique du chirurgien et de l'obstétricien. Il doit aussi avoir des connaissances étendues en pharmacologie, biochimie et biologie sans compter qu'il lui faut souvent avoir recours à la psychologie pratique. Pour les pionniers dans ce domaine les débuts n'ont pas été faciles puisqu'il y avait tout à faire. Aujourd'hui l'enseignement de l'anesthésie est bien organisé et sa pratique bien règlementée. Parmi les grands noms de l'anesthésiologie canadienne citons ceux de Easson Brown de Toronto et Wesley Bourne de McGill. L'évolution de la spécialité s'est déroulée dans les trois sphères d'activité suivantes: le développement de nouveaux médicaments et de nouvelles techniques d'administration; l'approfondissement des sciences de base en relation avec l'anesthésie et la fondation d'un enseignement de l'anesthésie.

Les deux plus grandes réalisations techniques semblent avoir été l'adoption du tubage intratrachéal et l'étude de la ventilation pulmonaire. Ces deux innovations sont intimement liées et, contrairement à ce que pourrait laisser supposer leur usage courant, ne datent que de quelques années. L'auteur accorde sa faveur à l'appareil le plus simple. Selon lui l'automation telle que représentée par cet instrument récent dont les circuits sont ouverts ou fermés selon les variations de l'électroencéphalogramme n'a pas sa place dans la salle d'opération. L'appareillage fondamental de l'anesthésie consiste en un laryngoscope, des tubes intratrachéaux, des manomètres et débimètres et un appareil pour assurer la ventilation pulmonaire. Les médicaments dont les propriétés anesthésiques ont été employés sont légion. Plusieurs d'entre eux ont été abandonnés et un certain nombre d'autres ne servent qu'à des fins spécialisées. L'auteur choisit de s'étendre sur deux d'entre eux au développement desquels il a contribué personnellement: le cyclopropane et le curare.

L'anesthésiste qui surveille un malade assailli par la maladie, par les médicaments et par l'intervention chirurgicale doit plus que tout posséder une bonne connaissance des sciences de base. L'état dans lequel le malade subit la chirurgie est loin d'être la reproduction du sommeil physiologique; il s'apparente plutôt à ce que le docteur John Gillies appelle "le trépas physiologique". Cet état comprend souvent de l'hypotension, de l'apnée et de la paralysie musculaire. La recouvrance facile et confortable que l'on prend maintenant pour acquise diffère considérablement des réveils orageux de jadis et justifie l'expansion des intérêts de l'anesthésiste.

L'enseignement de l'anesthésie au Canada date à peine de 15 ans. La guerre a souligné la pénurie de ces spécialistes et a donné l'erre d'aller à la formation de médecins dans ce domaine. L'élève en anesthésie doit maintenant suivre quelques années de cours post-universitaires et de résidence dans plusieurs hôpitaux. Il existe maintenant au moins 11 revues d'anesthésiologie publiées régulièrement dans différents pays. Les responsabilités attribuées à l'anesthésiste se sont accrues à mesure que ses connaissances augmentaient. On attend de lui aujourd'hui qu'il surveille l'oxygénothérapie, qu'il soit en charge des salles de recouvrance, qu'il fasse partie des banques de sang et des départements d'urgence. On se fie à lui dans les cas difficiles pour les injections intraveineuses, les ponctions lombaires, les intubations intratrachéales, les aspirations bronchiques, le contrôle des convulsions, la désintoxication des empoisonnements aux barbituriques, les blocs nerveux diagnostiques et thérapeutiques, les bronchoscopies d'urgence et les trachéotomies. On a même tendance dans certains milieux à le charger de responsabilités au cours de la période post-opératoire qui devraient être partagées avec le chirurgien traitant. L'auteur termine en énonçant une série de principes généraux tirés de son expérience de l'anesthésie et qui peuvent être appliqués à tous les domaines de la médecine.

CANADIAN JOURNAL OF SURGERY

The April 1960 issue of the *Canadian Journal of Surgery* contains the following original articles, short communication and case report:

History of Surgery: Foot binding in Chinese women—H. S. Y. Fang and F. Y. K. Yu.

Original Articles: Trauma to the head and associated ocular signs—F. B. Walsh, D. L. Knox in collaboration with R. Lindenberg. Anorectal lymphomas—J. Y. McGraw and J. L. Bonenfant. Infection following splenectomy in infants and children—A. D. Forward and P. G. Ashmore. Malignant melanoma of the skin: a valuable prognostic guide in the choice of cases for prophylactic lymph node dissection—F. V. Nicolle, W. H. Mathews and J. D. Palmer. Dry ice refrigeration of gangrenous limbs—F. R. C. Johnstone. A method of management of displaced fractures of the surgical neck of the humerus—I. A. D. Todd and J. E. Mullens. Imperforate anus with recto-vaginal fistula in an adult—P. H. Niloff, M. M. Gelfand and G. J. Strean. Strangulation of the appendix epiploica: a series of 11 cases—P. L. McGeer and A. D. McKenzie.

Short Communication: L'Equilibre hydroélectrolytique au lit du malade – J. Turcot et S. Plourde.

Case Report: Duodenum inversum – J. E. Anderson.

Canad. M. A. J.
April 23, 1960, vol. 82

RENAL AND CARDIOVASCULAR EFFECTS INDUCED BY INTRAVENOUS INFUSION OF MAGNESIUM SULPHATE*

H. GARFIELD KELLY, M.D., C.M., F.R.C.P.[C.], F.A.C.P.,† HECTOR C. CROSS, M.B., Ch.B.,‡ M. R. TURTON, M.D.§ and J. D. HATCHER, M.D., Ph.D.,¶ *Kingston, Ont.*

INTRODUCTION

IT HAS BEEN KNOWN for years that infusions of magnesium sulphate reduce blood pressure,[1-3] and it is thought that they do so by producing vasodilatation,[4, 5] largely through blockade of the sympathetic ganglia.[6, 7] Reports vary as to the extent to which renal vessels participate in the general vasodilatation, but there is some evidence to indicate that renal blood flow is maintained despite the fall in blood pressure, suggesting the possibility of renal vasodilatation.[8, 9]

This paper reports the effect of intravenous infusion of magnesium sulphate on blood pressure and renal function in both hypertensive and normotensive subjects.

METHODS

The patients used in this study were from the General and Ontario Hospitals in Kingston, Ontario. The first seven subjects of the series received a variable amount of magnesium sulphate (0.5-3.0 g.) injected as a 50% solution of magnesium sulphate, but it was soon found that this technique did not reliably produce a fall in blood pressure without undesirable side effects. When magnesium is injected too rapidly patients experience a feeling of intense warmth, usually accompanied by an unpleasant metallic taste in the mouth and sometimes by nausea and vomiting. Subsequent subjects were therefore infused with a standard dose of 8 g. of magnesium sulphate (containing 1.6 g. of magnesium) which was diluted in 250 ml. of normal saline and infused over a period varying from 50 to 80 minutes according to the patient's tolerance. This amount of magnesium caused no undue discomfort and regularly produced some degree of hypotension, but was often followed by a feeling of sleepiness.

The total period of study ranged from 1½ hours to 2½ hours, during which time the patient lay in a supine position. Blood pressure was measured through an indwelling intra-arterial needle by means of a Sanborn Electromanometer. Magnesium was not infused until blood pressure had remained constant for 15 to 20 minutes. Arterial samples were obtained before, during and after the infusion, for measurement of plasma magnesium and calcium levels. Calcium was measured because of the reported antagonism between the action of magnesium and calcium ions.[10, 11] In some instances, electrocardiograms were taken before the infusion, and later, at a time when it was considered that plasma magnesium might be at its peak level.

Later on in the series, renal studies were carried out concomitantly. In this series, hydration was achieved by giving the patient 100 ml. of water by mouth every 15 minutes, beginning an hour before the study, and continuing throughout the period of study in order to maintain a good urine flow. The total period of study comprised an initial equilibration period lasting 45 minutes after the injection of the priming dose of inulin and para-aminohippurate (PAH), a control period of 45 minutes, following which magnesium was infused for a period of approximately 30 minutes, and finally a post-infusion period of 30 to 45 minutes. Urine samples were collected every 15 minutes throughout the control, infusion and post-infusion periods. Blood samples were collected at the mid-point of each urine collection period through an indwelling arterial needle. Blood and urine samples were examined for inulin, PAH, magnesium, calcium, phosphorus, sodium, chloride and potassium. Glomerular filtration rate was estimated by the inulin clearance method of Roe and Epstein.[12] Renal plasma flow was measured by the clearance of PAH as described by Goldring and Chassis.[13] Plasma and urine magnesium values were measured initially by the method of Denis,[14] and later by the titan yellow method of Orange and Rhein.[15] Calcium determinations were carried out by the method of Carr and Frank;[16] phosphorus by the method of King and Wootton;[17] chlorides by the modified Sendroy technique.[18] Sodium and potassium levels were measured with a Coleman No. 14 flame photometer.

RESULTS

(a) *Cardiovascular Effects*

When magnesium sulphate is infused into the circulation, it produces a feeling of warmth, the intensity of which depends upon the rate of infusion. This effect is presumably the result of cutaneous vasodilatation which is usually, but not always, accompanied by a fall in blood pressure. The sort of hypotensive response which occurs is indicated in Table I which lists the data obtained in the study of the first 18 hypertensive and four normotensive subjects. The table shows that, in general, the faster the infusion rate and the higher the plasma magnesium level, the more pronounced

*From the departments of medicine and physiology, Queen's University.
Financed by a grant from the Department of National Health and Welfare through the Ontario Heart Foundation.
†Associate professor of medicine, Queen's University, Kingston, Ontario.
‡The Abbott Clinic, Winnipeg, Manitoba.
§Baker Clinic, Edmonton, Alberta.
¶Professor of physiology, Queen's University, Kingston, Ontario.
Special acknowledgment is made to Mr. Denis Craston for technical services.
Reprints may be obtained from Dr. H. Garfield Kelly, Etherington Hall, Queen's University, Kingston, Ontario.

TABLE I.—THE EFFECT OF $MgSO_4$ INFUSION ON BLOOD PRESSURE AND HEART RATE

Patient	*Total dose mg. Mg*	*Duration min.*	*Dose mg. Mg/kg./min.*	*Rise of plasma Mg mEq./l.*	*Fall of plasma Ca mEq./l.*	*Control B.P. mm. Hg*	*Change in B.P. mm. Hg*	*Control heart rate beats/min.*	*Change in heart rate beats/min.*
Hypertensives									
R.A.	101	75	0.02	+0.30	———	184/ 90	− 6/+ 2	—	——
C.S.	202	2	1.13	———	———	220/145	0/− 5	84	+ 6
R.S.	202	2	1.41	+0.53	———	196/105	− 8/— 5	60	+ 2
T.R.	303	3	1.85	+1.11	———	150/ 88	− 3/− 5	78	−
M.H.	303	3	2.18	+1.63	−1. 0	200/118	−22/−10	68	
J.T.	1010	66	0.19	+1.96	−0.55	164/ 92	− 9/− 3	90	− 2
N.T.	1287	55	0.29	+3.74	−0.30	185/102	−18/− 7	85	− 1
A.K.	1414	65	0.50	+5.07	−0.39	173/ 80	−23/−15	72	− 6
M.B.	1414	32	0.72	+4.37	−0.49	196/ 71	−24/−10	88	+ 3
H.D.	1414	20	1.07	+3.23	−0.46	162/ 90	−22/−10	—	——
N.T.	1616	53	0.35	+4.62	+0.60	185/ 91	+ 3/+ 4	76	0
E.S.	1616	83	0.25	+5.80	−0.76	245/117	−68/−39	72	0
J.V.	1616	56	0.40	+7.09	−0.25	206/127	− 6/ 0	80	+10
M.R.	1616	39	0.60	+5.31	−1.13	195/ 80	−87/−28	56	+ 3
R.G.	1616	55	0.46	+4.68	−0.14	240/ 97	−18/− 7	60	+10
M.B.	1616	58	0.45	+3.49	−0.57	175/ 76	+15/+ 6	70	+ 1
H.M.	1616	60	0.47	+9.31	−0.34	173/ 74	−35/− 3	72	+ 3
A.L.	1616	30	1.08	+5.00	+0.75	220/ 93	−40/−17	65	− 1
Normotensives									
G.S.	202	2	1.06	+0.53	———	140/ 76	0/+ 2	56	+ 2
A.F.	707	3.5	2.53	+2.05	−0.20	149/ 72	− 9/ 0	66	+ 2
C.T.	880	4.5	2.47	+2.01	−0.55	139/ 90	−11/−10	74	+ 8
R.P.	1616	30	0.73	+5.72	−1.10	124/ 81	+ 5/+ 3	51	+11

the fall in blood pressure. Heart rate does not change significantly.

The rise in plasma magnesium is accompanied by a fall in plasma calcium. Electrocardiograms were carried out in most of these cases, but no consistent change was noted. In a few instances, T voltage in the apical region diminished slightly, and in one instance, in which the electrocardiogram was already abnormal, a transient bundle-branch block developed.

Fig. 1 illustrates a typical response to the infusion of 8 g. of magnesium sulphate over a period of about 45 minutes. The infusion produced an abrupt but transient fall in blood pressure, and 15 minutes after the infusion had been completed, blood pressure had returned to near the pre-infusion level.

(b) *Effect on Renal Hæmodynamics*

In a further series, 10 hypertensive and seven normotensive subjects were similarly infused with magnesium sulphate, but in these subjects, renal function studies were carried out in conjunction with hæmodynamic measurements. Rates of infusion were adjusted so that a moderate hypotensive reaction recurred in about 50% of the hypertensive patients; this rate of infusion produced little or no change in the blood pressure of normotensive subjects. Data are presented in Table II.

In the hypertensive group, the infusion produced a significant percentage increase in glomerular filtration rate and renal plasma flow. After the infusion these values generally returned to control levels. In contrast, in the normotensive group there was a significant increase in renal plasma flow during the infusion, but not after; and there was no change in glomerular filtration rate, either during or after the infusion. It is of interest to note in the hypertensive group that glomerular filtration rate and renal plasma flow increased while blood pressure was falling, indicating in all probability renal vasodilatation.

(c) *Effect on Plasma Electrolytes*

The infusion of magnesium sulphate caused a variable rise in plasma magnesium level depending upon the speed of infusion; this was associated with a variable fall in plasma calcium. No change in the plasma level of other electrolytes was demonstrated. Data are presented in Table III.

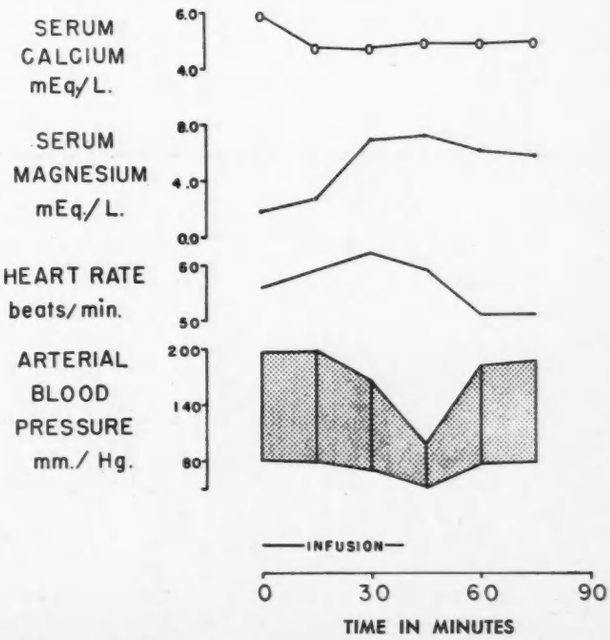


Fig. 1.—Effect of $MgSO_4$ (8.0 g. i.v.). Note the pronounced and transient fall in blood pressure, when plasma magnesium level is rising and calcium falling.

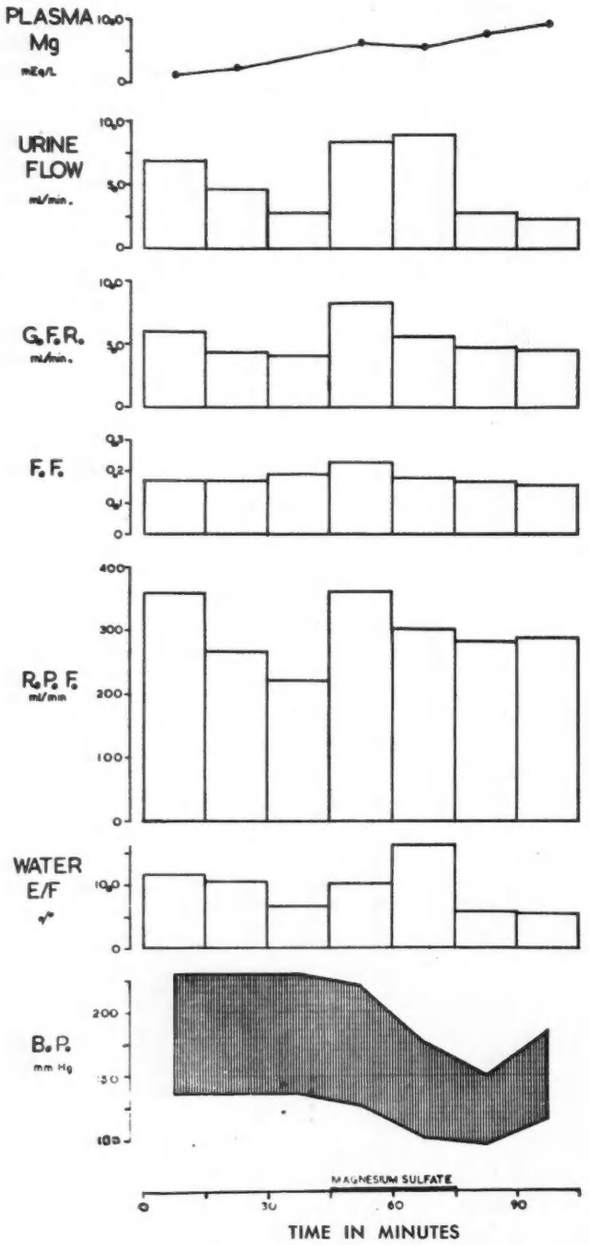


Fig. 2.—Effect of intravenous infusion of 8.0 g. of magnesium sulphate on renal hæmodynamics. Note the fall in blood pressure but sustained and even slightly increased urine flow, glomerular filtration rate and renal plasma flow.

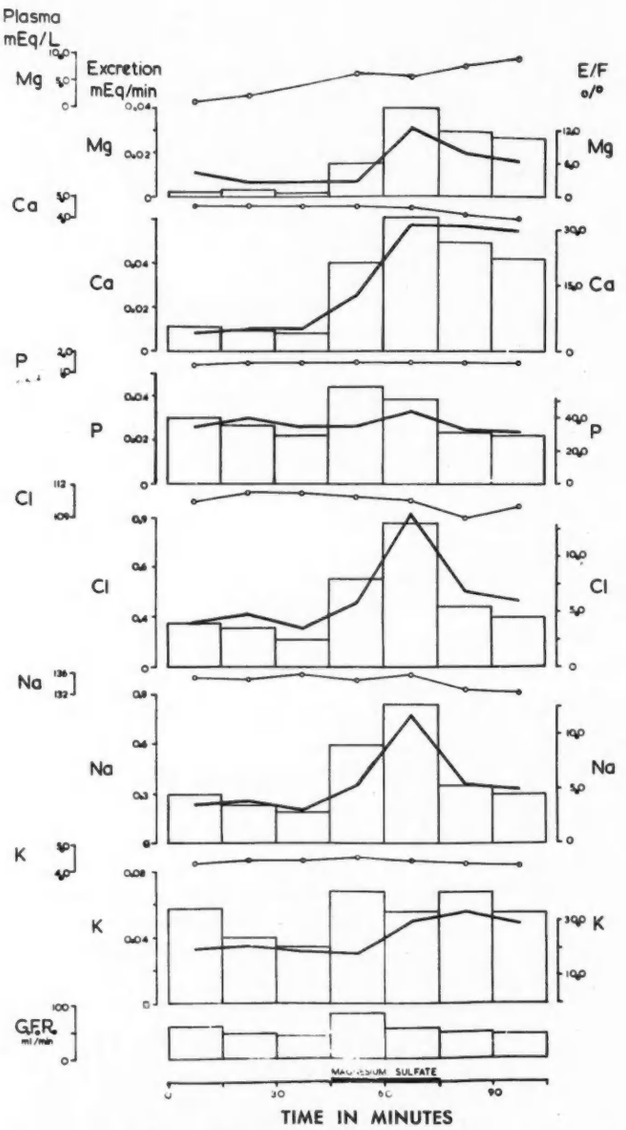


Fig. 3.—Effect of $MgSO_4$ infusion (8.0 g., i.v.) on plasma electrolyte levels, renal excretion of electrolytes, and glomerular filtration rate in a hypertensive subject.

(d) *Effect on Water and Electrolyte Excretion*

Table III also gives the data with respect to excretion of water and electrolytes. There was a marked increase in the excretion of magnesium, calcium, chloride and sodium, both during and after the infusion, although the increase in urine flow was limited in most cases to the actual infusion period. The normotensive subject excreted more sodium than the hypertensive subject. Potassium excretion was increased in the hypertensive but almost uniformly decreased in the normotensive. Phosphorus excretion was variable and unrelated to the excretion of other electrolytes. Although there was, on the average, at least some increase in the filtered loads of all electrolytes during the infusion period, the magnitude of their increased excretion was out of all proportion to changes in the filtered load, indicating altered tubular function.

Discussion

The data presented indicate that magnesium, if infused intravenously in large enough amounts, can bring about a fall in blood pressure that is much more marked in hypertensive than in normotensive subjects. However, this effect is transient, and the amount of magnesium required to produce it is relatively large, limiting its value as a therapeutic remedy except in emergencies. The subjective feeling of warmth and flushing which accompanies the infusion is clinical evidence of cutaneous vasodilatation; and the increased renal plasma flow that occurs in both normotensive and hypertensive subjects, whether or not there is any fall in blood pressure, is good evidence of renal vasodilatation. Glomerular filtration rate also in-

TABLE II.—EFFECT OF $MgSO_4$ INFUSION ON RENAL HÆMODYNAMICS IN HYPERTENSIVE AND NORMOTENSIVE SUBJECTS

Name		Increase in plasma Mg mEq./l.	B.P. mm. Hg S D	% change S D	Urine flow ml./min.	% change	G.F.R. ml./min.	% change	R.P.F. ml./min.	% change	F.F.	% change
Hypertensives												
	C*	———	236/129	———	8.3	———	149	———	588	———	.25	———
B.H.	D*	3.7	233/115	− 1.3/−10.9	10.5	+ 26.5	121	−18.8	545	− 7.3	.22	−12.0
	A*	———	190/110	−19.5/−14.7	4.5	− 45.7	97	−34.9	223	−62.1	.43	+72.0
	C	———	208/123	———	6.6	———	113	———	452	———	.25	———
F.Sc.	D	4.4	225/125	+ 8.2/+ 1.6	22.0	+233.3	120	+ 6.2	613	+35.2	.19	−24.0
	A	———	215/123	+ 3.4/ 0	12.3	+ 86.3	106	− 6.2	560	+23.9	.19	−24.0
	C	———	223/110	———	12.0	+ 45.0	68.9	———	265	———	.26	———
M.S.	D	8.5	198/ 92	−11.2/−16.4	17.4	− 45.0	74.1	+ 7.5	346	+30.6	.21	−19.2
	A	———	200/105	−10.3/− 4.5	6.6	———	45.6	−33.8	280	+ 5.7	.16	−38.5
	C	———	230/135	———	4.8	———	48.6	———	283	———	.17	———
W.L.	D	7.6	197/113	−14.3/−16.3	8.7	+ 81.2	69.5	+43.0	333	+17.7	.21	+23.5
	A	———	167/105	−27.4/−22.2	2.6	− 45.8	46.9	− 3.5	287	+ 1.4	.16	− 5.9
	C	———	231/124	———	12.4	———	66.2	———	245	———	.27	———
E.C.	D	2.5	227/123	− 1.7/− 0.8	14.5	+ 16.9	67.2	+ 1.5	246	+ 0.4	.27	+ 0.0
	A	———	236/124	+ 2.2/ 0	3.4	− 72.5	49.0	−25.0	175	−28.6	.28	+ 3.7
	C	———	244/162	———	4.6	———	25.5	———	88.4	———	.29	———
F.S.	D	4.1	235/155	− 3.7/− 4.3	4.8	+ 4.3	24.3	− 4.7	92.7	+ 4.9	.26	−10.3
	A	———	242/160	− 0.8/− 1.2	3.0	− 34.8	20.9	−18.0	75.6	−14.5	.28	− 3.4
	C	———	156/ 89	———	8.5	———	64.5	———	297	———	.22	———
E.B.	D	7.2	157/ 82	+ 0.6/− 7.9	8.7	+ 2.4	67.2	+ 4.2	245	−17.5	.27	−22.7
	A	———	150/ 72	− 3.8/−19.1	3.4	− 60.0	53.8	−16.6	245	−17.5	.22	———
	C	———	178/ 98	———	5.5	———	68.9	———	217	———	.32	———
W.D.	D	———	175/ 88	− 1.7/−10.2	14.7	+167.3	100.0	+45.1	231	+ 6.5	.43	+34.4
	A	———	190/105	+ 6.7/+ 7.1	9.3	+ 69.1	67.5	− 2.0	202	− 6.9	.33	+ 3.1
	C	———	240/100	———	9.4	———	47.6	———	257	———	.19	———
L.B.	D	———	175/ 75	−27.1/−25.0	14.9	+ 58.5	59.3	+24.6	310	+20.6	.19	———
	A	———	230/ 93	− 4.2/− 7.0	5.8	− 38.3	62.5	+31.3	261	+ 1.6	.24	+26.3
	C	———	175/ 76	———	9.6	———	94.1	———	450	———	.23	———
M.B.	D	———	172/ 72	− 1.7/− 5.3	13.4	+ 39.6	103.5	+10.0	501	+23.7	.21	+ 8.7
	A	———	185/ 81	+ 5.7/+ 6.6	8.0	− 16.7	127.9	+35.9	458	+13.1	.28	+21.7
	C	———	220/ 93	———	4.9	———	45.9	———	154	———	.30	———
A.L.	D	5.0	210/ 87	− 4.5/− 6.5	6.6	+ 34.7	60.1	+30.9	221	+43.5	.27	−10.0
	A	———	193/ 75	−12.3/−19.4	5.3	+ 8.2	50.4	+ 9.8	188	+22.1	.27	−10.0
			D	*A*	*D*	*A*	*D*	*A*	*D*	*A*	*D*	*A*
Average % change from control			−5.3/−9.3	− 5.9/− 5.0	+64.5	− 17.7	+13.4	− 5.8	+14.9	− 5.6	− 2.9	+ 4.1
S.D.			±9.3/±7.7	±10.1/±10.7	±72.4	± 51.9	±20.0	±23.8	±18.8	±24.8	±18.8	±29.0
S.E.M.			±2.8/±2.0	± 3.4/± 3.8	±21.8	± 15.6	± 6.0	± 7.2	± 5.7	± 7.5	± 5.7	± 8.7
Normals												
	C	———	120/ 70	———	10.6	———	90.4	———	483	———	.19	———
W.S.	D	3.5	118/ 65	− 1.7/− 7.1	14.8	+39.6	99.6	+10.2	614	+27.1	.16	−15.8
	A	———	125/ 75	+ 4.2/+ 7.1	9.6	− 9.4	81.2	−10.2	542	+12.2	.15	−21.1
	C	———	125/ 65	———	10.4	———	83.5	———	440	———	.19	———
R.S.	D	3.7	130/ 70	+ 4.0/+ 7.7	11.8	+ 13.4	87.3	+ 4.5	539	+22.5	.16	−15.8
	A	———	———	———	———	———	———	———	———	———	———	———
	C	———	105/ 80	———	10.3	———	78.9	———	444	———	.18	———
D.B.	D	5.9	118/ 78	+12.4/− 2.5	15.4	+ 49.5	83.7	+ 6.1	565	+27.3	.15	+16.7
	A	———	120/ 75	+14.3/− 6.3	4.4	− 57.3	53.4	−32.3	323	−27.3	.17	− 5.6
	C	———	122/ 80	———	11.6	———	86.5	———	560	———	.15	———
J.M.	D	4.3	123/ 78	+ 0.8/− 2.5	16.9	+ 45.7	101.2	+16.9	618	+10.4	.16	+ 6.7
	A	———	122/ 80	0/0	6.8	− 41.4	80.7	− 6.7	481	−14.1	.17	+13.3
	C	———	124/ 81	———	6.9	———	159.5	———	752	———	.21	———
R.P.	D	5.7	126/ 78	+ 1.6/− 3.7	9.5	+ 37.7	148.9	− 6.6	924	+22.9	.16	−23.8
	A	———	131/ 82	+ 5.6/+ 1.2	6.8	− 1.4	157.8	− 1.1	725	− 3.6	.22	− 4.8
	C	———	125/ 72	———	10.1	———	81.5	———	524	———	.16	———
C.B.	D	———	118/ 65	− 5.6/− 9.7	13.5	+ 33.7	81.3	− 0.2	570	+ 8.8	.14	− 1.5
	A	———	120/ 60	− 4.0/−16.7	4.8	− 52.5	92.2	+13.1	398	−24.0	.23	+43.8
			D	*A*	*D*	*A*	*D*	*A*	*D*	*A*	*D*	*A*
Average % change from control			+1.9/−3.0	+ 4.0/− 2.9	+36.6	− 32.4	+ 4.2	− 7.4	+19.8	−11.4	−13.0	+ 5.1
S.D.			±6.1/±6.0	± 6.9/+ 9.0	±12.7	± 25.5	± 8.2	±16.5	± 8.2	±16.1	±10.3	±24.8
S.E.M.			±2.5/±2.4	± 3.1/+ 4.0	± 5.2	± 11.4	± 3.3	± 7.4	±3.3	± 7.2	± 4.2	±11.1

*C, D and A refer to control, during, and after, infusion values.

creases in the hypertensive patient, leaving the filtration fraction unchanged, and suggesting that both the afferent and efferent limbs of the glomerular arterioles participate equally in the response. However, in the normotensive patient the glomerular filtration rate remains unchanged so that the filtration fraction actually falls, indicating a greater vasodilator effect on the efferent limb of the arteriole. This difference in response may be due to altered levels of basal tone in the glomerular arterioles in the hypertensive patient. It should be stressed though that these changes in renal hæmodynamics are modest in relation to the increases in electrolyte excretion discussed below.

The fall in plasma calcium level brought about by the infusion is unaccompanied by change in other plasma electrolytes, and is likely the result of diuresis of calcium. Womersley,[20] infusing much smaller amounts of magnesium sulphate (20 mEq.) into normal subjects, noted a similar increase in urinary calcium but no change in its serum level. The calcium diuresis is dependent upon the infusion of magnesium as a sulphate since subsequent work to be published, in which magnesium was

TABLE III.—EFFECT OF $MgSO_4$ INFUSION ON RENAL EXCRETION OF ELECTROLYTES

Name		Mg— mEq./min.	% Change	Ca— mEq./min.	% Change	P— mEq./min.	% Change	Cl— mEq./min.	% Change	Na— mEq./min.	% Change	K— mEq./min.	% Change
Hypertensives													
	C*	.010	———	.029	———	.071	———	.646	———	.671	———	.084	———
B.H.	D*	.108	+980.0	.106	+265.5	.023	−67.6	1.012	+56.7	.960	+43.1	.077	−8.3
	A*	.114	+1040.0	.124	+327.6	.050	−29.6	1.332	+106.2	1.178	+75.6	.092	+9.5
	C	.009	———	.016	———	.039	———	.500	———	.539	———	.053	———
F.Sc.	D	.156	+1633.3	.051	+218.8	.058	+48.7	1.424	+184.8	1.549	+187.4	.155	+192.5
	A	.143	+1488.8	.094	+487.5	.048	+23.1	1.505	+201.0	1.482	+175.0	.079	+49.1
	C	.015	———	.021	———	.031	———	.481	———	.494	———	.072	———
M.S.	D	.153	+920.0	.060	+185.7	.038	+22.6	1.027	+113.5	1.093	+121.3	.060	−16.7
	A	.203	+1253.3	.058	+176.2	.020	−35.5	.848	+76.3	.813	+64.6	.067	−6.9
	C	.002	———	.010	———	.026	———	.218	———	.232	———	.042	———
W.L.	D	.028	+1300.0	.050	+400.0	.042	+61.5	.695	+218.8	.714	+207.8	.072	+71.4
	A	.028	+1300.0	.045	+350.0	.023	−11.5	.333	+52.8	.323	+39.2	.061	+45.2
	C	.004	———	.010	———	.040	———	.456	———	.489	———	.089	———
E.C.	D	.109	+2625.0	.033	+230.0	.040	0	.828	+81.6	.922	+88.5	.083	−6.7
	A	.102	+2450.4	.034	+240.0	.014	−65.0	.563	+23.4	.536	+9.6	.093	+4.5
	C	.009	———	.012	———	.018	———	.345	———	.357	———	.037	———
F.S.	D	.054	+500.0	.023	+91.6	.018	0	.420	+21.7	.409	+14.6	.046	+24.3
	A	.078	+766.6	.025	+108.3	.014	−22.2	.367	+6.4	.339	−5.0	.047	+27.0
	C	.010	———	.008	———	.007	———	.205	———	.191	———	.042	———
E.B.	D	.094	+840.0	.021	+162.5	.005	−28.6	.288	+40.5	.268	+40.3	.031	−26.2
	A	.121	+1110.0	.035	+337.5	.012	+71.4	.413	+101.5	.420	+119.9	.024	−42.8
	C	——	———	.005	———	.030	———	.228	———	.231	———	.041	———
W.D.	D	——	———	.024	+380.0	.049	+63.3	.973	+326.8	1.091	+372.3	.067	+63.4
	A	——	———	.022	+340.0	.024	−20.0	.770	+237.7	.849	+267.5	.059	+43.9
	C	——	———	.007	———	.007	———	.317	———	.216	———	.029	———
L.B.	D	——	———	.034	+385.7	.013	+85.7	.884	+178.9	.935	+332.9	.043	+48.3
	A	——	———	.047	+571.4	.006	−14.3	.767	+142.0	.680	+214.8	.046	+58.6
	C	.002	———	——	———	——	———	——	———	.246	———	.066	———
M.B.	D	.088	+4300.0	——	———	——	———	——	———	.661	+168.7	.066	0
	A	.128	+6300.0	——	———	——	———	——	———	.792	+222.0	.055	−16.7
	C	.001	———	——	———	——	———	.125	———	.119	———	.041	———
A.L.	D	.031	+3000.0	——	———	——	———	.635	+408.0	.660	+454.6	.088	+114.6
	A	.045	+4400.0	——	———	——	———	.581	+364.8	.676	+468.1	.056	+36.7
		D	*A*	*D*	*A*	*D*	*A*	*D*	*A*	*D*	*A*	*D*	*A*
Average % change from control		+1788.7	+2204.3	+257.8	+326.5	+20.6	−99.6	+163.1	+131.2	+184.7	+151.0	+41.5	+18.9
S.D.		±3985.2	±1887.8	±109.4	±457.2	±48.8	±101.1	±81.6	±109.8	±85.3	±138.4	±101.2	±39.4
S.E.M.		±1328.4	±629.3	±36.5	±152.4	±16.2	±33.7	±25.8	±34.7	±29.0	±41.7	±31.1	±11.9
Normals													
	C	.015	———	.010	———	.011	———	.277	———	.435	———	.045	———
W.S.	D	.156	+940.0	.057	+470.0	.032	+190.9	.892	+222.0	1.574	+261.8	.017	−62.2
	A	.111	+640.0	.081	+710.0	.024	+118.2	1.038	+274.7	2.070	+375.9	.013	−71.1
	C	.017	———	.017	———	.038	———	.349	———	.307	———	.050	———
R.S.	D	.133	+682.4	.048	+182.4	.038	0	.841	+141.0	.838	+173.0	.033	−34.0
	A	——	———	——	———	——	———	——	———	——	———	——	———
	C	.010	———	.018	———	.042	———	.112	———	.085	———	.123	———
D.B.	D	.172	+162.0	.053	+194.4	.022	−47.6	.280	+150.0	.410	+382.4	.087	−29.3
	A	.211	+2010.0	.052	+188.8	.013	−69.0	.452	+303.6	.493	+480.0	.057	−53.7
	C	.003	———	.008	———	.004	———	.199	———	.150	———	.048	———
J.M.	D	.243	+8000.0	.057	+612.5	.008	+100.0	.761	+282.4	.709	+372.7	.042	−12.5
	A	.323	+10667.0	.053	+562.5	.007	+75.0	.879	+341.7	.817	+444.7	.039	−18.8
	C	——	———	——	———	——	———	.285	———	.321	———	.110	———
R.P.	D	——	———	——	———	——	———	.950	+233.3	1.020	+217.8	.125	+13.6
	A	——	———	——	———	——	———	1.048	+267.7	1.201	+274.1	.088	−20.0
	C	.007	———	.006	———	.006	———	———	———	.146	———	.074	———
G.B.	D	.164	———	.024	+300.0	.010	+66.6	———	———	.730	+400.0	.027	−63.5
	A	.253	———	.051	+750.0	.008	+33.3	———	———	.643	+340.4	.032	−56.7
		D	*A*	*D*	*A*	*D*	*A*	*D*	*A*	*D*	*A*	*D*	*A*
Average % change from control		+2446.1	+4439.9	+351.9	+552.8	+62.0	+39.4	+205.7	+296.9	+301.3	+383.0	−31.3	−44.1
S.D.		±3716.7	±4439.2	±57.2	±255.7	±92.1	±80.1	±59.6	±16.9	±96.3	±82.1	±29.6	±23.5
S.E.M.		±1858.4	±2566.0	±25.5	±127.9	±41.1	±40.1	±26.6	±8.5	±38.3	±36.7	±12.1	±10.5

*C, D and A refer to control, during, and after, infusion values.

infused as a chelate, failed to produce increased urinary excretion of calcium.[21] In the present study, larger amounts of calcium and magnesium were excreted by the normal than by the hypertensive kidney despite a proportionately smaller increase in glomerular filtration rate and urine flow. Sodium and chloride were also excreted in larger amounts by the normal kidney, an unexpected finding in view of the well-known tendency of the hypertensive kidney when stressed with an intravenous infusion of hypertonic or isotonic saline.[22-24] This tendency has been correlated roughly with the level of blood pressure and probably holds only as long as there is no significant reduction in renal function. Some of the subjects in this series had been hypertensive for many years, and reduced renal function may be a better explanation for their reduced response than any tendency for the magnesium sulphate to reverse the usual physiological action of an isotonic saline infusion. Both Heller,[19] using magnesium sulphate intramuscularly, and Womersley,[20] using it intravenously but in a much smaller dose (20 mEq.), demonstrated increased sodium excretion, but the latter found no chloride diuresis, a difference probably due to the smaller dose used. The diuresis of sodium and chloride, like that of calcium, is dependent upon the infusion of magnesium as a sulphate, since it does not occur with

magnesium chelate infusion.[21] While both the hypertensive and normal kidney handle sodium and chloride, calcium and magnesium, in a qualitatively similar fashion after an intravenous magnesium sulphate load, they deal with potassium quite differently. The hypertensive kidney excretes more potassium; the normotensive kidney less. The significance of this difference is not understood.

It is of interest that diuresis of water has accompanied that of electrolyte despite a fall in blood pressure which is normally an antidiuretic stimulus. Presumably the antidiuretic stimulus has been more than offset by the increased renal blood flow producing an effect similar to that which occurs when hydralazine or hexamethonium is infused.[25]

SUMMARY

Magnesium sulphate was infused intravenously in a group of hypertensive and normotensive subjects. When the dose was large enough it brought about a feeling of warmth and flushing, a fall in blood pressure and increased renal blood flow, all of which indicate generalized vasodilatation. The fall in blood pressure was more easily obtained and was more marked in hypertensive subjects.

Renal plasma flow was increased, and was accompanied by an increased glomerular filtration rate in hypertensive but not in normal subjects. These changes were slight.

The rise in plasma magnesium level was accompanied by a fall in plasma calcium but no change in other electrolytes. Renal tubular function was altered to produce increased urinary excretion of calcium, magnesium, sodium and chloride ions. Their excretion was more marked in normal than in hypertensive subjects. Potassium excretion was increased in hypertensives but almost uniformly decreased in normotensives. No consistent change in phosphorus excretion was noted. The water diuresis during the infusion was greater in normals.

The significance of these changes is discussed.

REFERENCES

1. ZOHMAN, B. L. AND STERNBERG, B.: *Ann. Int. Med.*, 7: 643, 1933.
2. WINKLER, A. W., SMITH, P. K. AND HOFF, H. E.: *J. Clin. Invest.*, 21: 207, 1942.
3. PRITCHARD, J. A.: *Surg. Gynec. & Obst.*, 100: 131, 1955.
4. HAURY, V. G.: *J. Pharmacol. & Exper. Therap.*, 65: 453, 1939.
5. *Idem*: *J. Lab. & Clin. Med.*, 24: 951, 1939.
6. ENGBAEK, L.: *Pharmacol. Rev.*, 4: 396, 1952.
7. STANBURY, J. B.: *J. Pharmacol. & Exper. Therap.*, 93: 52, 1948.
8. ETTELDORF, J. N. *et al.*: *A.M.A. Am. J. Dis. Child.*, 83: 301, 1952.
9. HELLER, B. I., HAMMERSTEN, J. F. AND STUTZMAN, F. L.: *J. Clin. Invest.*, 32: 858, 1953.
10. MELTZER, S. J. AND AUER, J.: *Am. J. Physiol.*, 21: 400, 1908.
11. BRYANT, G. W., LEHMANN, G. AND KNOEFEL, P. K.: *J. Pharmacol. & Exper. Therap.*, 65: 318, 1939.
12. ROE, J. H., EPSTEIN, J. H. AND GOLDSTEIN, N. P.: *J. Biol. Chem.*, 178: 839, 1949.
13. GOLDRING, W. AND CHASSIS, H.: Hypertension and hypertensive desire, Commonwealth Fund, New York, 1944, p. 203.
14. HAWK, P. B., OSER, B. L. AND SUMMERSON, W. H.: Practical physiological chemistry, 12th ed., The Blakiston Company, Philadelphia, 1947, p. 593.
15. ORANGE, M. AND RHEIN, H. C.: *J. Biol. Chem.*, 189: 379, 1951.
16. CARR, M. H. AND FRANK, H. A.: *Am. J. Clin. Path.*, 26: 1157, 1956.
17. KING, E. J. AND WOOTTON, I. D. P.: Micro-analysis in medical biochemistry, 3rd ed., J. & A. Churchill Ltd., London, 1956, p. 75.
18. SENDROY, J., JR.: *J. Biol. Chem.*, 120: 405, 1937. *Idem*: *Ibid.*, 127: 483, 1939.
19. HELLER, B. I., HAMMARSTEN, J. F. AND STUTZMAN, F. L.: *J. Clin. Invest.*, 32: 858, 1953.
20. WOMERSLEY, R. A.: *Clin. Sc.*, 15: 465, 1956.
21. KELLY, H. G., CROSS, H., TURTON, R. C. AND HATCHER, J. D.: To be published.
22. FARNSWORTH, E. B.: *J. Clin. Invest.*, 25: 897, 1946.
23. GREEN, D. M. *et al.*: *Circulation*, 6: 919, 1952.
24. BIRCHALL, R. *et al.*: *Ibid.*, 7: 258, 1953.
25. EK, J., BUCHT, H. AND WERKÖ, L.: *Am. Heart J.*, 48: 102, 1954.

RÉSUMÉ

L'infusion intraveineuse de sulfate de magnésium à un groupe de sujets hypertendus et normaux a causé chez eux une sensation de chaleur et de suffusion, une chute de tension artérielle et une augmentation de la circulation rénale qui semblent être les signes d'une vasodilatation généralisée. La chute de tension fut plus prononcée et obtenue plus facilement chez les hypertendus que chez les autres. Le flot plasmatique rénale augmenta et ne fut accompagné d'un taux plus élevé de filtration glomérulaire que chez les hypertendus seulement. Ces variations furent minimes. L'élévation du taux de magnésium sanguin fut accompagnée d'une chute du taux de calcium mais ne semble pas avoir affecté la concentration des autres électrolytes. Au cours de l'expérience la fonction tubulaire rénale s'est adaptée à une excrétion augmentée du calcium, du magnésium, du sodium et des chlorures urinaires. Cette tendance fut plus marquée chez les sujets normaux que chez les hypertendus. L'excrétion potassique fut augmentée chez les hypertendus mais non chez les sujets normaux. L'excrétion du phosphore demeura inchangée mais la diurèse aqueuse fut plus marquée chez les sujets normaux que chez les autres.

TEAMWORK

We must put to rest, once and for all, the archaic beliefs that public health physicians should confine themselves to preventing illness and that private practitioners should limit themselves to curative medicine. It has become rather obvious today that the continuum of prevention, treatment, and rehabilitation is a job requiring the closest possible teamwork among private medical practitioners, public health physicians, and those in official and voluntary health and social welfare agencies. This partnership can also be valuable in helping to dispel the undue worrying about illness that dims life's enjoyment for too many people. Many people today are too conscious of illness and not conscious enough of what they can do to avoid it.—Hon. Nelson A. Rockefeller: *Am. J. Pub. Health*, 50: 12, 1960.

AIR POLLUTION

Dr. Leslie B. C. Trotter writes to the *British Medical Journal* (1: 281, 1960) as follows: "In the campaign for clean air in cities what strikes one as remarkable is the omission of all reference to the internal combustion engine. It is rather like 'Hamlet' without the Prince of Denmark. It does not require much imagination to realize the amount of poisonous vapour discharged by motors just ticking over in a traffic jam. This does not occur merely in foggy weather but at all times. . . . There is far less smoke in the atmosphere than there was at the end of last century."

Canad. M. A. J.
April 23, 1960, vol. 82

STUDIES ON A NEW HYPOTENSIVE AGENT: BRETYLIUM TOSYLATE*

J. GENEST, M.D., F.A.C.P., F.R.C.P.[C.],
C. DUFAULT, M.D., G. PIGEON, M.D.,†
J. DAVIGNON, M.D.,† P. BIRON, M.D.,† and
J. TRUDEL, M.D.,† *Montreal, Que.*

TREATMENT OF arterial hypertension has been in constant progress since the discovery of the hypotensive effects of hexamethonium by Paton and Zaimis in 1948.[1] In May 1959, a new drug, bretylium tosylate, became available for clinical evaluation in patients with arterial hypertension. Results obtained indicate that this new sympathetic blocking drug constitutes an important improvement in the medical treatment of hypertension because of its effectiveness and the almost complete absence of parasympathetic blocking action.

Bretylium tosylate is a benzyl quaternary ammonium compound (Fig. 1), synthetized by Boura

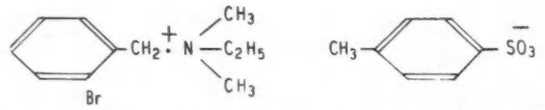


Fig. 1.—Structural formula for the para-toluene sulfonate salt of bretylium tosylate.

and co-workers at the Wellcome Research Laboratories in 1959,[2] and presented as a para-toluene sulfonate salt. This drug has a selective blocking action on the peripheral ortho-sympathetic nerves, resembling that following section of adrenergic nerves. It has little or no significant effect on parasympathetic function. Pharmacological studies with C^{14}-labelled bretylium tosylate indicate that it is only partially absorbed by the alimentary tract and that higher levels of radioactivity are found in sympathetic ganglia, post-ganglionic sympathetic fibres and organs with a rich adrenergic innervation than in any other tissues of the body.

Boura, Rosenheim and co-workers[3] using a colour reaction for determination of bretylium tosylate have demonstrated that only 10-30% of the drug administered orally to humans was recovered in the urine. On the other hand, Dollery and co-workers,[4, 5] using the C^{14}-labelled drug, found that the total excretion of the compound after an oral dose in humans ranged from 5 to 18% with a mean of 13%, within the following 24 hours.

PATIENTS AND METHODS

Our study includes 41 patients of whom 14 were men and 27 were women. The mean age was 49 years with a range of 18 to 66. Thirty patients presented with essential hypertension, five with renal hypertension and six with malignant hypertension. The mean period of administration of the drug was 16 weeks with a range of three to 29 weeks (from June 1959 to January 1960).

The 41 patients included in this study were divided into four groups. The first group included 14 patients already receiving hypotensive drugs, including ganglionic-blocking agents, either mecamylamine* or pempidine.† This group was followed up for an average period of 15 weeks (with a range of four to 24 weeks) for the specific purpose of comparing the side effects and effectiveness of the new drug with those of the ganglionic-blocking agents. The average dose of bretylium tosylate was 1200 mg. per day (with a range of 400 to 2700).

TABLE I.—DETAILS OF STUDY OF BRETYLIUM TOSYLATE (DARENTHIN)

Pre-Darenthin control period	*Darenthin period*	*No. of patients*	*Average period (weeks) of administration*
			Range
Patient already receiving hypotensive drug(s)	+	14	15 (4-24)
No drug	+	15	18 (3-28)
No drug	Dar. + thiazide	12	16 (8-29)
No drug	Dar. + thiazide + hydralazine (Apresoline)	3	19 (14-28)

The three other groups had control periods during which no drug was given. This control period consisted of either four to 24 weeks' follow-up in our Hypertension Clinic or the average of 28 hourly readings taken during the first two days of hospital stay. Group 2 included 15 patients‡ receiving bretylium tosylate alone for an average period of 18 weeks with a range of three to 28 weeks. The average diastolic pressure during the control period was 115 mm. Hg for both recumbent and upright position. The average dose of bretylium tosylate was 725 mg. per day (with a range of 300 to 1200).

Group 3 was made up of 12 patients with a severer degree of diastolic hypertension than those of group 2. Patients in this group received bretylium tosylate and chlorothiazide or one of its derivatives for an average period of 16 weeks, with a range of eight to 29 weeks. The average diastolic pressure during the control period was 122 mm. Hg. The mean dosage of bretylium tosylate was 800 mg. per day, with a range of 500 to 1200.

*From the Clinical Research Department, Hôtel-Dieu Hospital, Montreal.
This work was supported through a grant from Burroughs Wellcome & Company.
Bretylium tosylate (Darenthin) was generously provided through the courtesy of Dr. J. R. Bogert, Burroughs Wellcome & Company, Montreal.
†National Research Council Medical Research Fellow, 1959-60.

*Trade name: Inversine. Generously provided through the courtesy of Dr. Levasseur, Merck & Company, Montreal.
†Trade name: Pempiten. Generously provided through the courtesy of Dr. Blondel, Charles E. Frosst & Company, Montreal.
‡Three patients from this group later received bretylium plus one or both of the other two medications mentioned for groups 3 and 4. Each patient was treated long enough to belong to two groups, hence a total of 44 observations.

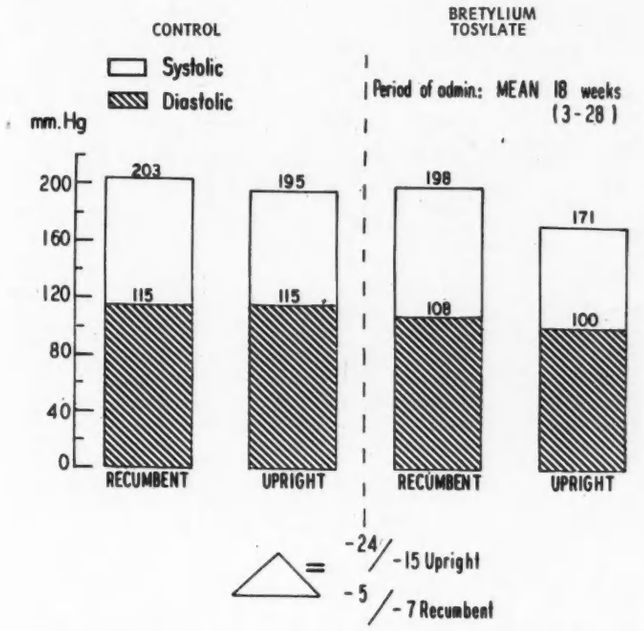


Fig. 2.—Effect of bretylium tosylate alone on blood pressure of 15 hypertensive patients. The average dosage of bretylium tosylate in this group was 725 mg. per day with a range of 300 to 1200.

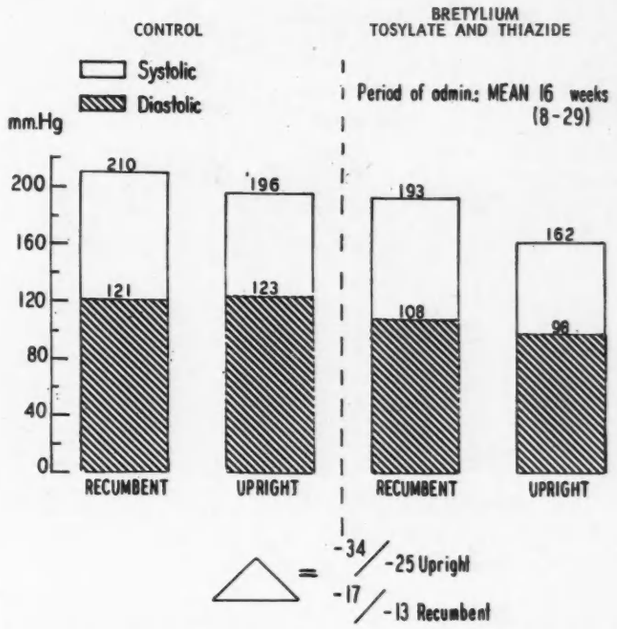


Fig. 3.—Effect of bretylium tosylate and thiazide on blood pressure of 12 hypertensive patients. The mean dosage of bretylium tosylate was 800 mg. per day with a range of 500 to 1200.

Group 4 included three severe hypertensive patients with an average diastolic pressure of 135 mm. Hg during the control period. These patients received bretylium tosylate and chlorothiazide or one of its derivatives, and hydralazine (Apresoline*) for an average period of 19 weeks (with a range of 14 to 28 weeks). Mean dosage of bretylium tosylate was 900 mg. per day, with a range of 600 to 1200.

RESULTS

It is not easy to assess objectively the results of such a study because of differences during control periods and during the periods of administration of bretylium tosylate. It is also difficult to assess the effects of concomitant emotional or other stressing factors in a given individual during the course of his treatment. Expressing results in terms of decrease in diastolic pressure has little value if this decrease, for example of 20 mm. Hg, in diastolic pressure means a lowering from 150 to 130 mm. Hg; but it is meaningful if this decrease has been from 110 to 90 mm. Hg. We prefer to report our results as mean decreases in systolic and diastolic pressures, both in upright and recumbent positions, of the four groups in which patients have been studied under similar conditions.

Results obtained in group 2, which was made up of 15 hypertensive patients receiving bretylium tosylate alone, are illustrated in Fig. 2. During the average period of administration of the drug of 18 weeks, the mean fall in blood pressure was significant only with the patient in the upright position, with a decrease of 24/15 mm. Hg. Little change occurred in blood pressure with the patient in the recumbent position. Better results could have been achieved in this group, if it had not been for a few patients who were studied in the early phase of our investigation of bretylium tosylate and who developed unexpected attacks of orthostatic hypotension. At that time it was thought wiser to prevent such attacks in patients with hypertension complicated by atherosclerosis by administering other hypotensive agents in order to permit better control and less fluctuation of blood pressure.

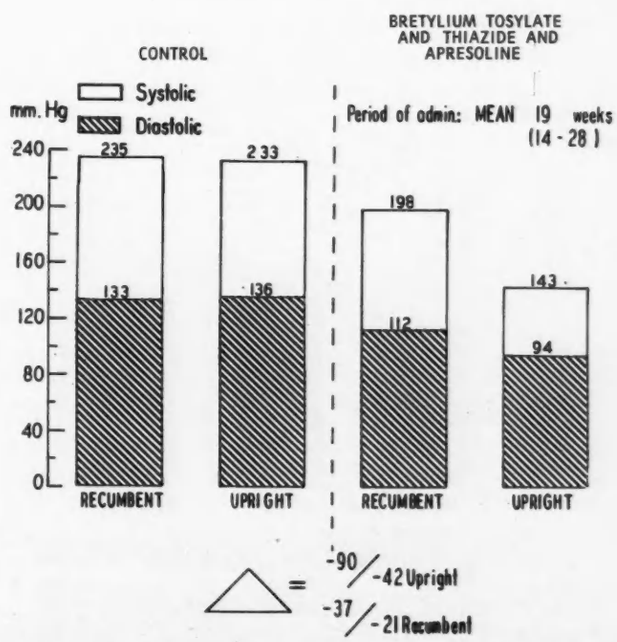


Fig. 4.—Effect of bretylium tosylate and thiazide and hydralazine on blood pressure of three hypertensive patients. The mean dosage of bretylium tosylate in these patients was 900 mg. per day with a range of 600 to 1200 mg. per day.

*Kindly provided through the courtesy of Dr. Walter Murphy, Ciba Co., Montreal.

Canad. M. A. J.
April 23, 1960, vol. 82

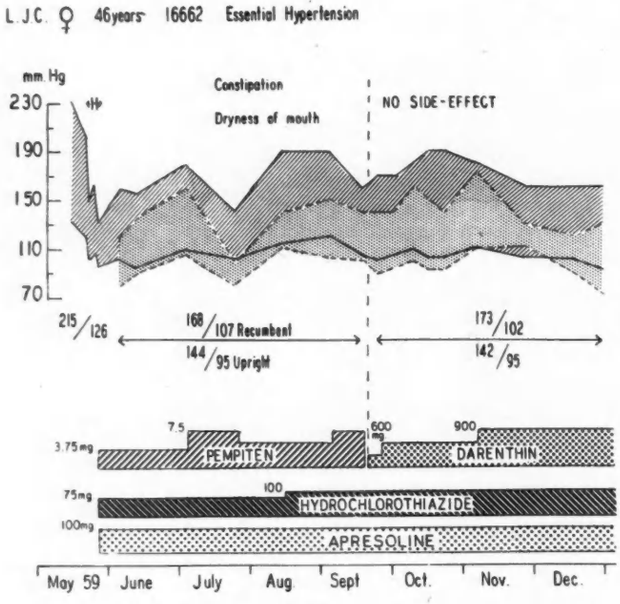


Fig. 5.—Illustrates the absence of parasympathetic blocking effects of bretylium tosylate as opposed to pempidine.

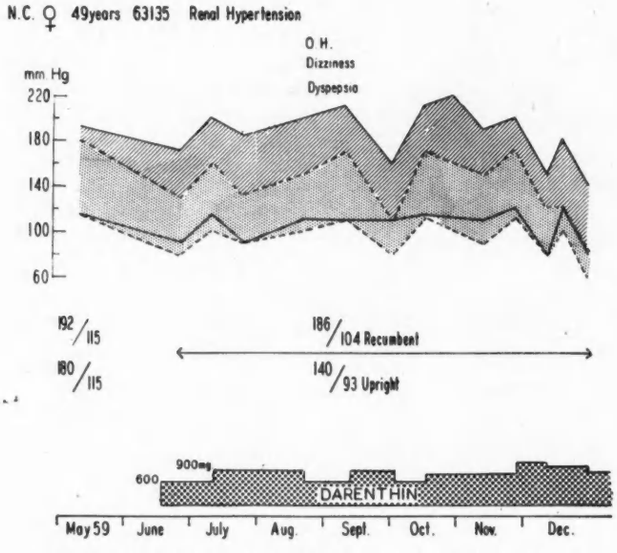


Fig. 7.—Significant fall in blood pressure in a patient with benign renal hypertension, especially marked when the patient was in upright position.

Results obtained in group 3, made up of 12 hypertensive patients receiving bretylium tosylate and one of the thiazide derivatives for an average period of administration of 16 weeks, are shown in Fig. 3. It is obvious that the fall in blood pressure was much more marked than that for group 2 who were receiving bretylium tosylate alone. The mean decrease in blood pressure, with the patient in the upright position, was 35/25 mm. Hg and, in the recumbent position, 17/13 mm. Hg. The addition of a natriuretic agent of the thiazide series obviously potentiates the hypotensive effect of bretylium tosylate.

Results obtained for group 4, consisting of three severely hypertensive patients who received bretylium tosylate, chlorothiazide or one of its derivatives and apresoline for an average of 19 weeks, are illustrated in Fig. 4. The combination of the three drugs produces impressive results, especially marked when patients are in the upright position, with an average fall of 90/42 mm. Hg. With patients in recumbent position, the decrease in blood pressure is 37/21 mm. Hg. These results show that bretylium tosylate is an effective hypotensive agent, the more so when the patient is in the upright position. Hypotensive effects of bretylium tosylate are markedly potentiated by its combination with a natriuretic drug, such as one of the thiazide derivatives, alone or with hydralazine.

The main advantage of the ortho-sympathetic blocking drug is the almost complete absence of any marked para-sympathetic blocking effect. This has been noted repeatedly in the patients included in group 1 and those previously treated with hypo-

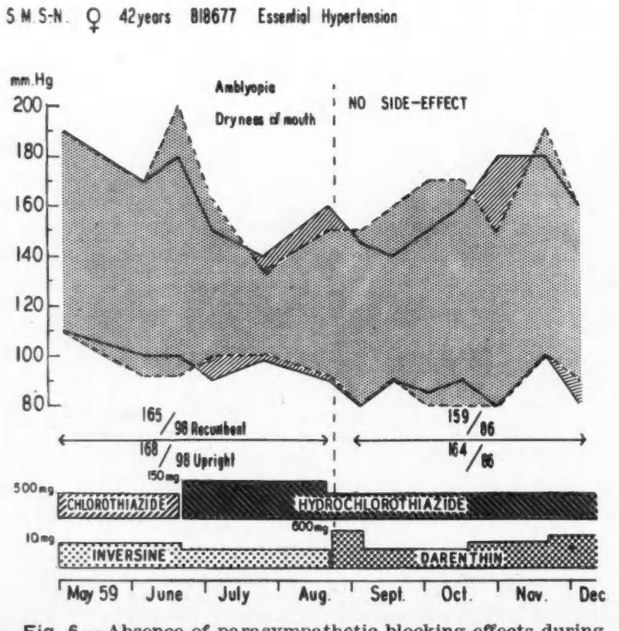


Fig. 6.—Absence of parasympathetic blocking effects during bretylium tosylate administration (in contrast to mecamylamine).

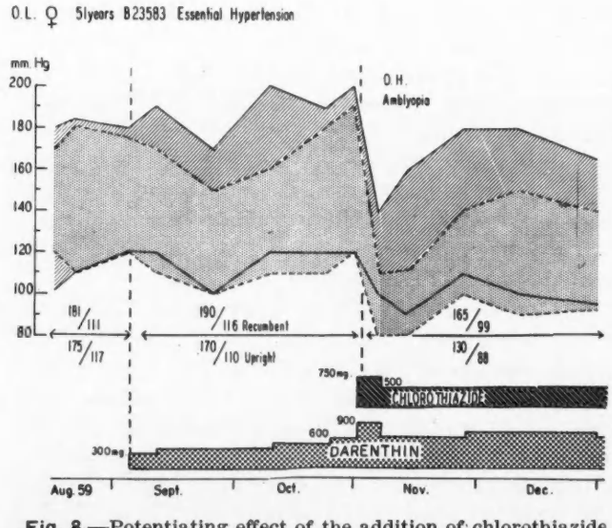


Fig. 8.—Potentiating effect of the addition of chlorothiazide to bretylium tosylate with lowering of the blood pressure in upright position to normal levels.

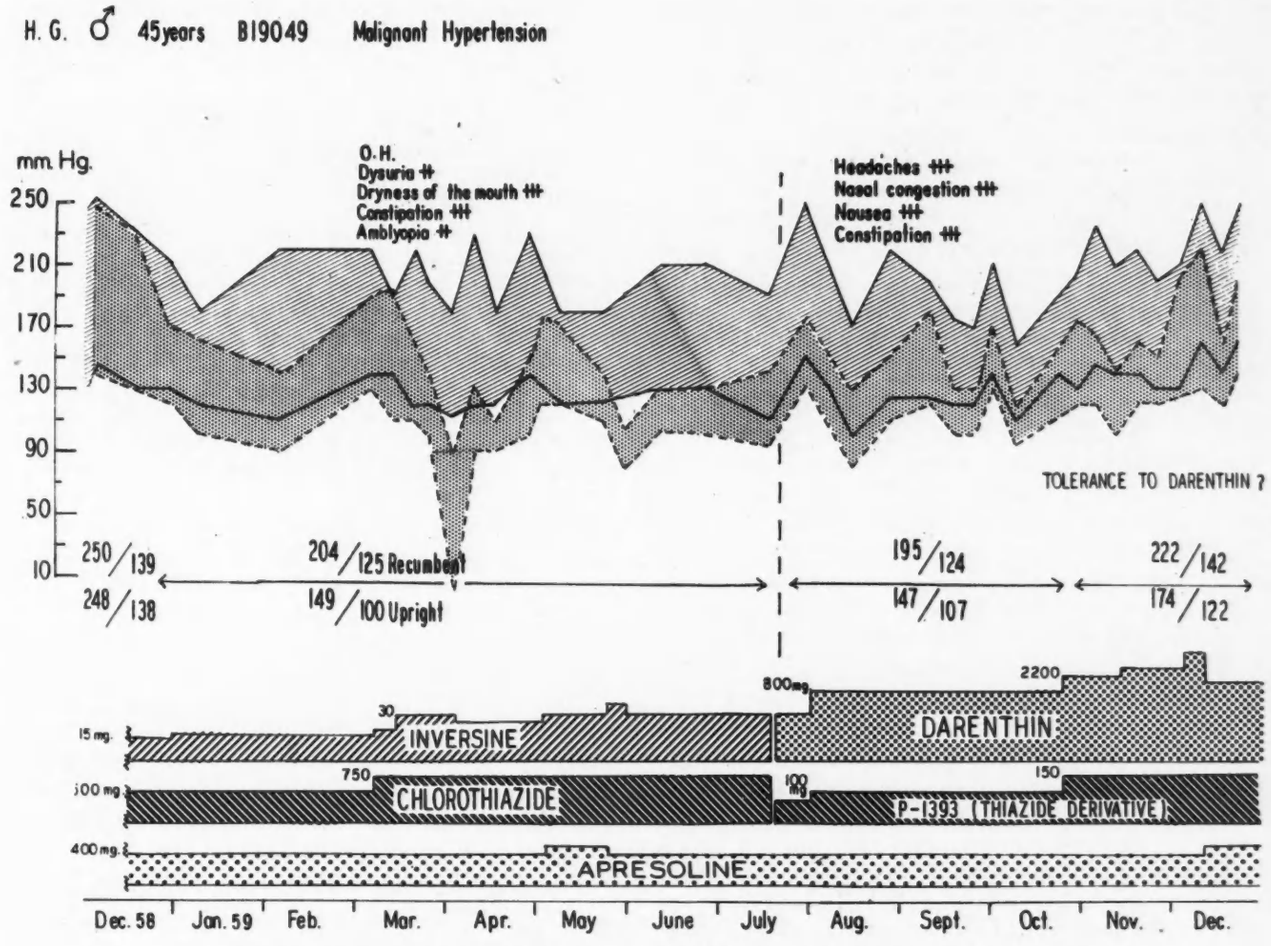


Fig. 9.—Example of probable tolerance to bretylium tosylate. This patient suffered from malignant hypertension with accompanying severe renal failure and uræmia.

tensive drugs, including mecamylamine or pempidine.

Substitution of bretylium tosylate for the ganglionic-blocking agent is always accompanied by a disappearance of or a marked decrease in ganglionic-blocking effects. Fig. 5 illustrates the case of a 46-year-old woman with a controlled blood pressure of 215/126 mm. Hg in recumbent position. Combined administration of pempidine, hydrochlorothiazide and hydralazine brought the blood pressure to normotensive levels in the upright position and produced a marked decrease in both systolic and diastolic levels with the patient in recumbent position. During this period, the patient complained repeatedly of constipation and dryness of mouth. After four months of combined treatment, pempidine was replaced by bretylium tosylate, the other two drugs, hydrochlorothiazide and hydralazine, being maintained at the same dosage. Blood pressure remained approximately the same as in the previous months, but the patient did not complain of any side effects attributable to the blocking of the para-sympathetic system.

Another illustration of this is the case of a 42-year-old woman with essential hypertension (Fig. 6). Before bretylium tosylate was given, the patient was on a combined therapy of mecamylamine and chlorothiazide or hydrochlorothiazide. During four months of administration of these two drugs, blood pressure was fairly well controlled, with an average diastolic pressure of 98 mm. Hg compared to a control pressure of 125 mm. Hg taken the year before treatment with mecamylamine and chlorothiazide was started. Substitution of bretylium tosylate for mecamylamine produced a further decrease in diastolic pressure to 86 mm. Hg, both in upright and recumbent positions, and complete disappearance of side effects previously noted by the patient.

Bretylium tosylate alone was administered to a 49-year-old patient with renal hypertension during a seven and one-half month period. It lowered his blood pressure to normal levels in the upright position and produced a significant fall in pressure in the recumbent position (Fig. 7). During administration of bretylium tosylate, dosage had to be decreased on two occasions from 900 to 600 mg. a day, because of repeated dizziness, orthostatic hypotension and complaints of dyspepsia.

Addition of a natriuretic drug, such as chlorothiazide, to bretylium tosylate greatly potentiates the hypotensive effect (Fig. 8). In this case, where the control blood pressure was 181/111 mm. Hg in recumbent position and 175/117 mm. Hg in

Canad. M. A. J.
April 23, 1960, vol. 82

upright position, administration of moderately small doses of bretylium tosylate during two months produced little change in blood pressure. But addition of chlorothiazide to bretylium tosylate brought the blood pressure to normal levels in the upright position and brought about a significant fall in the recumbent position. During this period of combined treatment, the patient complained of orthostatic hypotension and slight blurring of vision.

An example of probable tolerance of bretylium tosylate is that of a 45-year-old woman with malignant hypertension (Fig. 9). Her control blood pressure was 250/139 mm. Hg in recumbent and 248/138 mm. Hg in upright position. For seven months, the patient received a combination of mecamylamine, chlorothiazide and apresoline, which produced an average fall in blood pressure to 149/100 mm. Hg in upright position. During this period, the patient complained repeatedly of orthostatic hypotension, dysuria, dryness of the mouth, constipation and slight blurring of vision. Bretylium tosylate was substituted for mecamylamine, the thiazide derivative and hydralazine being kept at the same dosage as previously. There was little change in blood pressure during the first three months of administration. Some of the patient's complaints, such as headache and nausea, could be due to the presence of uræmia and severe renal failure. Nasal congestion and blurring of vision were probably due to administration of bretylium tosylate. In the last two months of administration, despite the repeated increases in bretylium tosylate dosage to 2800 mg. per day, the blood pressure rose progressively higher and higher. This appears to be an instance of tolerance to bretylium tosylate.

At no time during this investigation were efforts made to push the dosage of bretylium tosylate to the limit of tolerance. Whenever a dosage of 1.2 to 1.5 g. per day was reached and there had been little or an inadequate effect on the blood pressure, another drug, usually a natriuretic compound, was added. Because of the occurrence of unexpected attacks of orthostatic hypotension (also noted by other workers[4-6]), it was thought best to prevent such sudden attacks in patients with severe hypertension and associated atherosclerosis by adding another drug to bretylium tosylate. In this way, sudden attacks of postural hypotension were decreased in frequency.

SIDE EFFECTS

The side effects noted during the study of bretylium tosylate and their incidence are listed in Table II. The most frequent are dizziness and a state of excessive fatigue when the patient was in upright position. This was noted in 12 patients. As mentioned before, orthostatic hypotension was seen in 10 other patients and occurred sometimes unexpectedly, probably because of an increase in intestinal absorption.[3, 5] Nine patients had various digestive complaints ranging from anorexia, vague dyspepsia, nausea and flatulence to pain in the right hypochondrium. Three patients complained of decrease in libido and two of them of inhibition of ejaculation. Four had pain over the parotid and masseter regions, which were like muscle cramps and were especially marked when eating. This was also noted by Dollery and coworkers.[4, 5] No explanation can be given for these pains. Four patients had a slight degree of dryness of the mouth. This may be a sign that this drug produces at least a slight blocking of the parasympathetic function. Euphoria was observed in two patients. This euphoria may be associated with the disappearance of side effects of previously administered ganglionic-blocking agents.

TABLE II.

Side effects	*41 patients*
Dizziness	12
Orthostatic hypotension (sometimes unexpected)	10
Digestive complaints (anorexia, dyspepsia, nausea, flatulence, pain over right hypochondrium)	9
Decrease in potency	6
Slight dryness of mouth	4
Headaches	4
Nasal congestion	3
Amblyopia	3
Decrease in libido	3
Lower maxillary pains	4
Inhibition of ejaculation	2
Palpitations	2
Euphoria	2

Bretylium tosylate has the disadvantage of having a very bad taste and of being hygroscopic. This latter necessitates keeping the pills in glass or metallic containers. High dosage is sometimes necessary for adequate control of blood pressure, which means daily ingestion of 10 to 15 tablets, in addition to other hypotensive drugs that may have to be taken simultaneously.

In five patients, bretylium tosylate had to be discontinued. One refused the drug, because of repeated postural hypotension caused by excessive dosage. A second developed a tachycardia of 160 per minute with palpitations and postural hypotension. Unassociated hepatic failure led to cessation of the drug in a third patient. The last two patients died suddenly during treatment. Both had a similar history and clinical picture of retrosternal pain. In the first patient the pain occurred mostly after meals and after walking, and was not alleviated by nitroglycerin. His electrocardiographic tracing was normal, both at rest and after exercise (Master's test). He had been taking bretylium tosylate at a dosage of 1200 mg. daily for four months, along with a thiazide derivative.*

The second patient had a history of a retrosternal feeling of heaviness of two years' duration, which came on while walking and did not radiate or give rise to shortness of breath. His electrocardiographic tracing was normal at rest. At time of death, he had been taking bretylium tosylate, 600 mg. daily, for

*Pfizer, P-1393.

a period of six months, along with the same thiazide derivative* as the other patient.

SUMMARY

Investigation of bretylium tosylate in 41 patients over an average period of administration of 16 weeks confirms the first reports of Boura, Rosenheim and coworkers.[3] The drug was effective in lowering blood pressure, particularly with the patient in the upright position. Addition of a natriuretic drug of the thiazide series, singly or with hydralazine, greatly enhances the hypotensive action of bretylium tosylate. Another great advantage of this new ortho-sympathetic blocking compound, apart from its potent hypotensive effect, is the almost complete absence of parasympathetic blocking effect. Tolerance to the drug appeared to develop in one patient in our series.

The generous collaboration of Misses Fernande Salvail, R.N., Renée Dansereau, R.N., Pierrette Bourque, R.N., and Louise Hirbour, R.N., is gratefully acknowledged.

REFERENCES

1. PATON, W. D. M. AND ZAIMIS, E. J.: *Nature*, 162: 810, 1948.
2. BOURA, A. L. A., COPP, F. C. AND GREEN, A. F.: *Ibid.*, 184: 70, 1959.
3. BOURA, A. L. A. *et al.*: *Lancet*, 2: 17, 1959.
4. DOLLERY, C. T.: *Practitioner*, 184: 116, 1960.
5. DOLLERY, C. T., EMSLIE-SMITH, D. AND MCMICHAEL, J.: *Lancet*, 1: 296, 1960.
6. SMIRK, S. H. AND HODGE, C. V.: *Ibid.*, 2: 673, 1959.

RÉSUMÉ

Un nouvel hypotenseur le tosylate de bretylium fut mis à l'essai dans le département des recherches cliniques de l'Hôtel-Dieu de Montréal. Ce composé quaternaire d'ammonium dont la synthèse fut réalisée en mai 1959 par Boura au laboratoire de recherches de la Burroughs-Wellcome semble posséder une action confinée au sympathique et son retentissement sur le parasympathique est presque nul. Il n'est absorbé que partiellement dans les voies alimentaires. On l'administra à une série de 41 hypertendus d'un âge moyen de 49 ans dont 30 souffraient d'hypertension essentielle, cinq de forme rénale et six de forme maligne. La période d'administration s'étendit sur une durée moyenne de 16 semaines (de 3 à 29) et la posologie quotidienne varia de 400 à 2700 mg. (1200 mg. en moyenne). Cette série de malades fut divisée en quatre groupes, le premier était formé de 14 malades, déjà sous traitement, recevant des hypotenseurs; on s'en servit comme groupe témoin afin de comparer les résultats et les effets secondaires du traitement. Les 15 malades du second groupe ne reçurent que du bretylium. On observa chez eux une chute moyenne de tension de 24/15 mm. de mercure accompagnée dans plusieurs cas d'hypotension orthostatique. Le troisième groupe composé de 12 malades atteints d'hypertension plus grave reçut du bretylium accompagné de chlorothiazide ou de l'un de ses dérivés. L'apport de ce composé natriurétique renforça considérablement l'action hypotensive du bretylium, si bien que la chute de tension en position debout fut de 35/25 et de 17/13 dans la position couchée. Les trois malades du quatrième groupe avaient une tension diastolique moyenne de 135 avant le traitement; ils reçurent en plus du bretylium et du chlorothiazide, de l'aprésoline. Cette combinaison produisit un abaissement impressionant de la tension artérielle de l'ordre de 90/42 dans la position debout et 37/21 en décubitus. Lorsque le bretylium remplaça les ganglioplégiques, les effets secondaires causés par l'interruption du parasympathique comme la constipation et la sécheresse de la bouche disparurent. L'administration de bretylium donna lieu à des étourdissements et à un état de fatigue excessive chez 12 malades lorsqu'ils se tenaient debout. On nota aussi de l'anorexie, une certaine dyspepsie, des nausées, de la flatulence et des douleurs dans l'hypochondre droit dans neuf cas. Certaines douleurs dans la région des parotides et des masséters se manifestant au cours de la mastication ont déjà été observées sans toutefois recevoir d'explication satisfaisante. En plus de posséder un goût très désagréable, le médicament est hygroscopique et doit être conservé dans des contenants à l'épreuve de l'humidité.

*Pfizer, P-1393.

CLINICAL EXPERIENCE WITH BRETYLIUM TOSYLATE*

J. A. LEWIS, M.D., F.R.C.P.[C.], F.A.C.P.,†
London, Ont.

THE POSSIBILITY of reduction of blood pressure in the hypertensive by sympathectomy to permit pooling of blood in the large vascular reservoir, was foreseen by Rowntree and Adson.[1] Surgeons, including Peet,[2] Smithwick[3] and Grimson,[4] selected the abdominal visceral pool and report a percentage improvement by various degrees of splanchnic sympathetic denervation.

Paton and Zaimis[5] introduced in the ganglionic blocking agent, hexamethonium, a drug of sufficient potency and duration of effect to be of practical, although tedious, therapeutic value. Intensive investigation has produced several agents[7, 8] with similar pharmacological properties, varying among themselves from mecamylamine, which is totally absorbed and crosses the spinal fluid barrier, to pentolinium which is incompletely and irregularly absorbed and of sufficient molecular size to be excluded from the spinal fluid circulation.

These agents have common side effects, which include pupillary dilatation, bowel and bladder paresis and, frequently, loss of sexual potency. All add to the discomfort of the patient, occasioned by postural hypotension and possible syncope. Although Genest and Rosenheim[11] report differences between drugs in this series in the dominant side-effects, we[12] have observed the side effects to vary from patient to patient and in proportion to the height of the dosage, rather than between the chemical members of the ganglionic blocking group. These drugs have also in common the property of marked enhancement of hypotensive effect by the addition of hydrochlorothiazide or chlorothiazide to the therapeutic regimen.[6] While repre-

*From the Heart Service, Westminster Hospital, Department of Veterans Affairs, London, Ontario.
†Chief of Service, Medicine, Westminster Hospital, Department of Veterans Affairs, London, Ontario; Assistant professor of medicine, University of Western Ontario.

Canad. M. A. J.
April 23, 1960, vol. 82

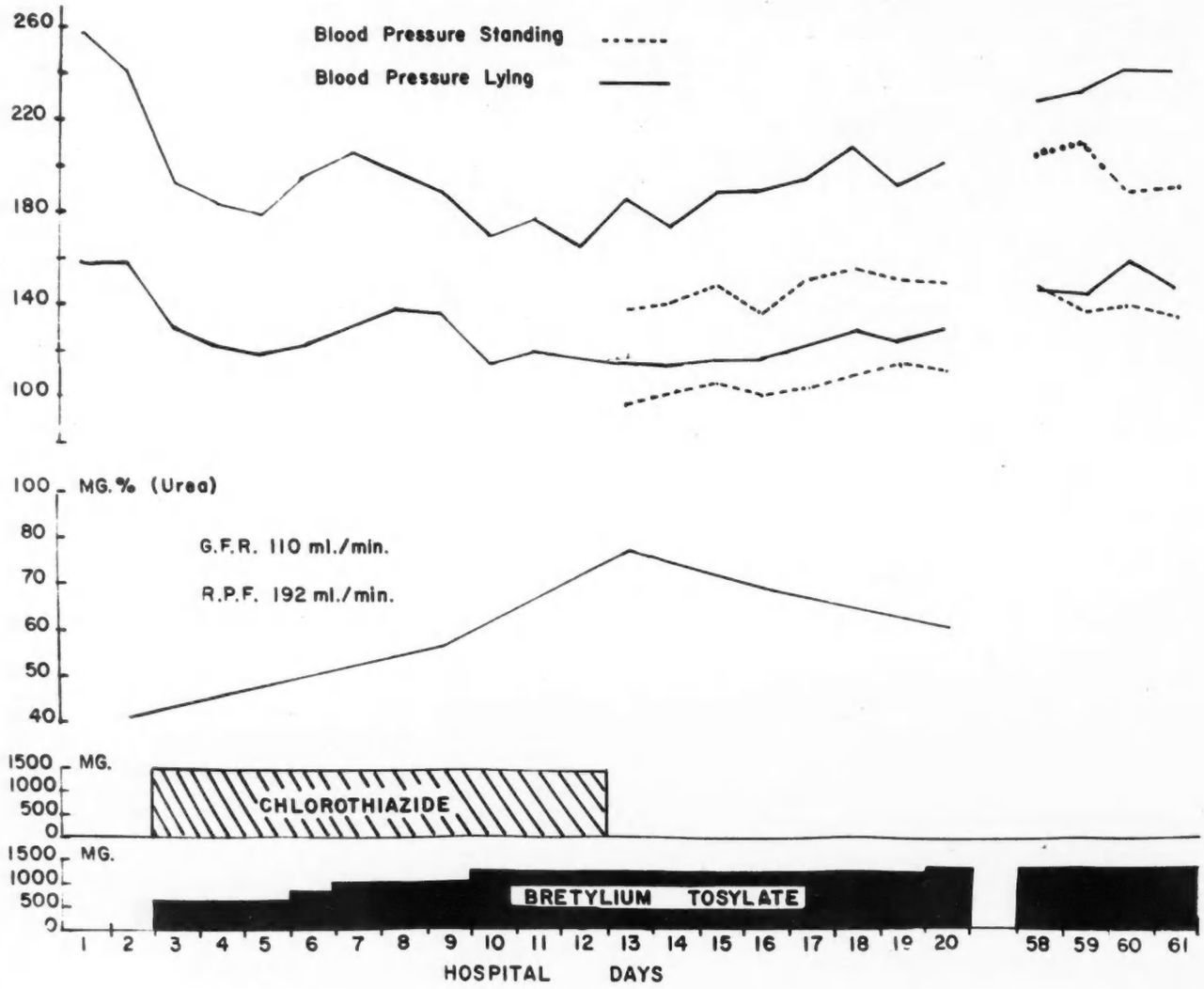


Fig. 1.

senting gratifying progress in the medical treatment of hypertension, the incidence of uncomfortable to frankly disabling, and even dangerous, side effects, detracts from the subjective results of treatment. The therapeutic goal of specific sympathetic interruption was not achieved.

Boura, Copp and Green[9] reported on studies of the series of benzyl quaternary ammonium compounds which selectively block the peripheral sympathetic nervous system without antagonizing the effects of adrenaline or noradrenaline. The pharmacological and therapeutic report published in *Lancet*[10] indicates the practical nature of this compound, now designated as bretylium tosylate. In theory this compound should not reduce bowel or bladder motility, but its effect upon gastric acid secretion might be of significance.

Since September 5, 1959, ten patients were treated with this drug.* Three had been receiving a ganglionic blocking agent (mecamylamine) and were suffering varying degrees of partially disabling side effects before admission for substitution with bretylium tosylate. This change resulted in marked subjective improvement in vision and bowel and bladder function. As an example, one patient had required a nightly laxative and was unable to read because of blurring of his vision. Upon substitution of bretylium he returned to his natural bowel habit, read and took part in active physiotherapy and occupational therapy. Subsequent epigastric fullness, vomiting and constipation have aggravated his pre-existing uræmia and necessitated suspension of bretylium therapy. Return of sexual potency lost by two patients on mecamylamine has resulted from this substitution. In none of these ten patients have meteorism and urinary slowing to retention been observed.

CASE 1.—S.M., aged 54, was admitted in congestive heart failure with a blood presure of 215/130 mm. Hg, and averaging 200/125. The fundi were normal; the heart large, with first-degree heart block; but no azotæmia, and with known diverticulitis. Patient was started on bretylium on September 14, at which time

*Through the kindness of Burroughs Wellcome & Company of Canada and Dr. J. R. Bogert, generous supplies of bretylium were placed in the Heart Service of the Department of Medicine at Westminster Hospital.

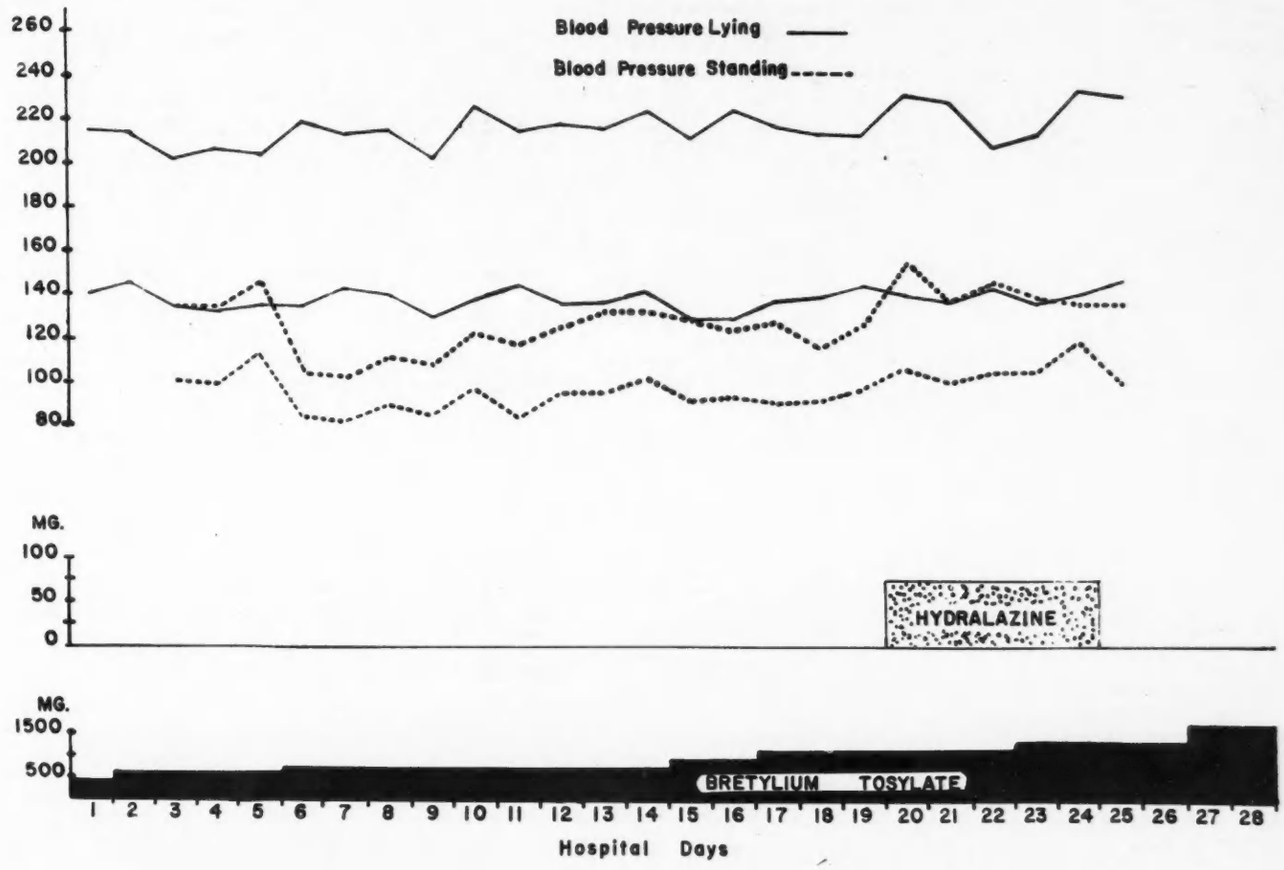


Fig. 2.

the blood pressure fell progressively to an average of about 150/95 mm. Hg lying and 145/80 standing, with one episode of hypotension of 115/40. The congestive failure required continued administration of mercurial diuretics. There was no blurring of vision, no constipation and no urinary symptoms. The patient was discharged on bretylium 200 mg. t.i.d.

CASE 2.—H.L., aged 38, was admitted with hypertension, possibly secondary to chronic glomerulonephritis. Previous management included hydralazine 75 mg. q.i.d., and mecamylamine 1.25 mg. t.i.d., increasing to 10 mg. daily. On admission (October 5), blood pressure was 210/140, with grade 2 fundi; no cardiac enlargement; Hb. value 10 g.; blood urea level 114 mg. %, with 2 plus albumin. Patient had been having severe trouble with constipation and had some urinary retention. With the commencement of bretylium therapy the lying blood pressure was variable but the standing blood pressure showed a marked drop. His lying blood pressure is less well controlled; the diastolic value averaging perhaps 130 with the standing B.P. being about 110/80. There has been a steady improvement in his subjective complaints. He is able to read; requires no laxative and has no hesitancy in passing his urine.

CASE 3.—A.K., aged 58, was admitted September 3, as a rheumatoid arthritic; otherwise asymptomatic, but with B.P. 235/150, the diastolic reaching 178 at times. The fundi showed marked arteriolar spasm and small spots of exudate. The heart was large and heaving, with no evidence of failure; normal electocardiogram. The blood urea value was 42 mg. %; urinary specific gravity, 1.014, and urine contained 1 plus albumin. On September 6 he was started on bretylium 200 mg. t.i.d. and chlorothiazide 1 g. per day. The lying B.P. dropped on this dose to 170/110 mm. Hg but gradually rose, necessitating an increase in the dosage of bretylium. By September 23 the urea value had risen to 78 and the chlorothiazide was discontinued; a drop in his urea to 60 occurred at the time of discharge, without any apparent alteration in the control of the B.P. About September 15 the blood pressures were recorded as averaging about 185/120 lying and 130/100 standing. Again there was no constipation, blurring of vision or urinary symptoms. This man has been readmitted, with B.P. response as described, for determination of endogenous creatinine clearance and electrolyte and water clearance.

CASE 4.—N.B.B., aged 44, was admitted October 13 with increasing headaches and blurred vision. His eyegrounds are grade 4; B.P. 250/160: the heart slightly enlarged with no murmur or gallop and no congestive failure. This man represented a treatment failure with mecamylamine and a medical emergency with malignant hypertension. Bretylium was begun in 200 mg. doses by mouth. Within four hours the B.P. was recorded at 220/155 lying but 155/115 standing. The following day it had reached 200/130 lying, and the standing pressure was 130/98. His fluid output was not grossly changed. Blood pressure levels rose in spite of progressive increase in the dose of bretylium to a total of 3.4 g. per day. Hydralazine in 150 mg. doses daily produced no enhancement of the hypotensive effect.

Canad. M. A. J.
April 23, 1960, vol. 82

TABLE I.—SUMMARY OF THE PERTINENT DATA FROM 10 PATIENTS

Patient	*A.K.*	*LA.*	*SM.*	*FE.*	*NT.*
Age	58	50	54	41	40
Sex	M.	M.	M.	M.	M.
B.P.	230/130	184/130	220/140	200/140	200/130
Fundi	2+	2+	1+	2+	2+
ECG	L. axis	L. strain	L. hyper	L. axis	L. strain
Urine	Alb. tr. casts	1.016 Alb. neg.	Alb. 3+	Alb. 1+ few casts	Alb. neg. 1.015
Blood urea	60	27	30	30	33
B.P. standing	140/90	130/100	180/100	150/100	130/100
lying	220/130	180/120	190/90	180/110	180/130
Bretylium dosage	2 g.	1.3 g.	700 mg.	600 mg.	2 g.
Other agents	chlorothiazide	promazine	Digitalis, diuretics, chlorothiazide	Nil	Nil
Associated diseases	Arthritis	Nil	Prostatism	Obesity	Nil
Urea clearance	—	—	—	88.9	92

Patient	*HA.*	*SH.*	*H.L.*	*HE.*	*N.B.B.*
Age	66	53	38	24	44
Sex	M.	M.	M.	M.	M.
B.P.	240/120	230/120	240/150	196/130	250/160
Fundi		3+	2+	2+	4+
ECG	L. strain	L. strain	L. strain	L. strain	L. strain
Urine	1.016 Alb. tr.	1.012 Alb. neg.	4+ alb. gran. casts	3+ alb. gran. casts	Alb. tr. few gran. casts
Blood urea	48	21	174	60	42
B.P. standing	190/90	150/100	185/135	130/100	170/125
lying	260/115	190/115	230/150	210/145	268+/175
Bretylium	1.4 g.	600 mg.	2.2 g.	1.25 g.	3.3 g.
Dosage				1 g.	2.1 g.
Other agents	Nil	Insulin	Hydralazine	Reserpine I.M.	Reserpine I.M. now added, hydralazine
Associated diseases	Prostatism	Diabetes	Nephritis	P. nodosa	
Urea clearance	66				

After seven days of this dosage of bretylium he noticed unsteadiness of gait, a knot in his stomach and vomiting. Constipation existed without meteorism. Meanwhile his vision had deteriorated to appreciation of light and dark only. Bretylium was then discontinued until vomiting had ceased and was resumed in a dosage of 600 mg. t.i.d. in conjunction with chlorisandamine (Ecolid) 20 mg. twice daily. Response to this therapy was unsatisfactory. The patient's condition steadily deteriorated and death occurred outside this hospital.

Fig. 1 (Case 3) is an example of postural hypotensive effect with maintenance of satisfactory therapeutic range of the recumbent blood pressure. Also shown in this figure is the apparent lack of pharmacological enhancement by the addition of chlorothiazide, observed in a total of three patients in whom this combination was studied. The low glomerular filtration rate (inulin clearance) and renal plasma flow (para-aminohippuric acid clearance) should be noted. Note also the increase in blood urea and the subsequent fall after cessation of chlorothiazide, despite maintenance of therapeutic lowering of blood pressure with bretylium.

Fig. 2 shows a less satisfactory therapeutic response. Note the marked drop in standing blood pressure with persistence of marked elevation of the blood pressure in the recumbent position. Note also that the addition of hydralazine produced no alteration of the blood pressure level.

Table I summarizes the pertinent data of these ten patients. Sufficient time has not elapsed to permit observations of late side effects, for example, interstitial pneumonia, seen with the prolonged use of hexamethonium. To this date few side effects have been observed. When profound postural hypotension has existed, faintness has been common. There has been no alteration in the usual bowel habit of the individual when dosage was below 2.5 g. per day, except in the three patients recently receiving mecamylamine, in whom the use of laxatives was no longer required. No hesitancy in urination has been observed, and pupillary size and reaction have remained unchanged. One patient (S.M.) complained of cessation of sweating. There was no significant slowing of the pulse. Two patients on a daily dose in excess of 2.5 g. report a cramp in the epigastrium with a feeling of unsteadiness in gait, followed by obstipation. Two further patients have reported weakness in the legs on walking: one at a distance of 100 yards; another after one flight of stairs. This is accompanied by no change in reflexes.

In contrast to the reported findings of Professor Rosenheim[11] and Smirk,[13] the addition of chlorothiazide and hydralazine produced in this small series no enhancement of blood pressure lowering effects of bretylium tosylate. It is our impression in three cases at least, one of whom is shown in Fig. 2, that the orthostatic effect with bretylium may be more pronounced than with ganglionic blocking agents. This is a disadvantage, since postural syncope may occur whilst the recumbent blood pressure remains at an undesirably high level.

The freedom from hazard of tympanites and urinary retention permits use of this potent antihypertensive drug in circumstances where ganglionic blocking agents pose difficulty or danger. In the older patients with hypertension and failure, in nephritics with malignant hypertension, and in at least one man with sufficient prostatic obstruction to be of clinical significance, the use of bretylium tosylate has not given rise to unexpected complications.

CONCLUSION

Bretylium tosylate therapy would appear on the basis of this brief experience to be a significant advance in the treatment of hypertension; certain annoying to semi-disabling side effects produced by ganglionic blocking agents are not correspondingly significant when this drug is used. Pharmacological effects appear to be confined to sympathetic nerve interruption within the dosage limits used in this study. Subjective muscular weakness has been noted in two patients; in two others, digestive symptoms of undetermined cause, followed by vomiting and obstipation, occurred at relatively high dose. The possible presence of hyperchlorhydria from relative vagal predominance has not yet been investigated. It is stressed that in this short period of study no serious side effects have been observed, but in view of the short period of observation, this finding must be interpreted with caution.

May I acknowledge my gratitude to Dr. E. A. Fergusson, hospital superintendent, Drs. W. J. M. Cameron, G. W. Manning and M. M. Mosbaugh, and the Clinical Investigation Unit for their assistance and co-operation.

REFERENCES

1. ROWNTREE, L. G. AND ADSON, A. W.: *J. A. M. A.*, **85**: 959, 1925.
2. PEET, M. M.: *Univ. Hosp. Bull., Ann Arbor*, **1**: 17, 1935.
3. SMITHWICK, R. H.: *Surgery*, **7**: 1, 1940.
4. GRIMSON, K. S.: *Ann. Surg.*, **114**: 753, 1941.
5. PATON, W. D. M. AND ZAIMIS, E. J.: *Brit. J. Pharm. & Chemotherapy*, **4**: 381, 1949.
6. SMIRK, F. H., DOYLE, A. E. AND MCQUEEN, E. G.: *Lancet*, **2**: 159, 1954.
7. GRIMSON, K. S.: *J. A. M. A.*, **158**: 359, 1955.
8. DEMING, Q. B. *et al.*: *New England J. Med.*, **256**: 739, 1957.
9. BOURA, A. L. A., COPP, F. C. AND GREEN, A. F.: *Nature*, **184**: 70, 1959.
10. BOURA, A. L. A. *et al.*: *Lancet*, **2**: 17, 1959.
11. ROSENHEIM, F. AND GENEST, J.: Personal Communication.
12. LEWIS, J. A.: Unpublished observations.
13. SMIRK, F. H. AND HODGE, J. V.: *Lancet*, **2**: 673, 1959.

RÉSUMÉ

En vertu de ses effets secondaires négligeables, le tosylate de bretylium semble marquer une étape importante dans le traitement de l'hypertension. Les effets pharmacologiques de ce nouveau médicament paraissent confinés à l'interruption du système nerveux sympathique dans les limites de la posologie employée au cours de cette présente étude. Parmi les 10 malades qui en ont reçu, deux se sont plaints de fatigue musculaire subjective et deux autres de symptômes digestifs de cause indéterminée suivis de vomissements et de constipation tenace lorsque la dose fut augmentée. Il se pourrait que l'hyperchlorhydrie causée par une prédominance vagale relative soit à la source de ces désordres mais l'auteur n'a pas poussé ses recherches dans cette direction. Au cours de cette courte période d'administration, aucun effet secondaire sérieux n'a été observé.

Case Reports

RENAL AND CEREBRAL SCLERODERMA*

F. M. BOURNE, M.D., F.R.C.P.[C.],†
D. A. HOWELL, M.B., M.R.C.P.(Lond.)‡ and
HOWARD S. ROOT, M.D.,§ *Montreal*

SCLERODERMA is now well established as a general systemic disease, so much so that the name progressive systemic sclerosis has been suggested. The following case is reported because of particular findings in two systems. The patient presented with an apparent nephrotic syndrome; this picture has previously been reported, but is uncommon. In the last few days of life, mental confusion and finally convulsions and coma occurred. Again, such symptoms have been reported, but are rare. At autopsy the kidneys, as well as some other organs, showed well-developed vascular changes of scleroderma. In the brain, there was an encephalopathy associated with similar vascular changes.

The patient, a 34-year-old housewife of Scottish origin, was admitted on January 27, 1957, to the Montreal General Hospital. She had had a cold at Christmas time, 1956, and then about January 17, 1957, she developed generalized œdema, an itching skin rash, burning micturition, nausea and vomiting and insomnia. On January 25, the family physician found that she was hypertensive and recommended admission.

She denied any illness before this last one. Aside from taking calomel on January 23, and occasional doses of castor oil, she had no history of exposure to drugs. She considered herself allergic to chocolate, which had caused nausea and vomiting on occasion, and was made rather ill by eating turkey.

After her death, it was learned from another physician that about 1941 her Wassermann test had been found positive in successive tests over some months, and that she had received full treatment with arsenic and bismuth for presumed syphilis. There was no

*From the Departments of Medicine and Pathology, Montreal General Hospital.
†Associate physician.
‡Assistant neurologist.
§Assistant pathologist.

TABLE I.—BLOOD CHEMISTRY

	January 28	*January 30*	*January 31*	*February 4*	*February 8*	*February 14*
Blood sugar (mg. %)	93.0					
Blood urea nitrogen (mg. %)	22.0		26	29.0	25.0	28
Creatinine (mg. %)	1.1					
Serum protein (g. %)	3.7			3.6	3.3	
Albumin (g. %)	0.7			0.65	0.5	
Globulin (g. %)	3.0			3.0	2.8	
CO_2 comb. power (mEq./l.)	32.0					18
Serum cholesterol (mg. %)		307				
Serum bilirubin (mg. %)				0.1		
Serum sodium (mEq./l.)					128.0	
Serum potassium (mEq./l.)					4.1	

history of primary luetic infection, and her husband's serology is thought to have been negative.

On admission she appeared to be about her stated age, well nourished, with obvious œdema of face, sacrum and legs. Blood pressure was 210/100 mm. Hg, pulse 80 and regular. Over the back, chest, buttocks and thighs were seen target-shaped macules with white centres. These tended to spread and become less distinct in outline as the days went by. A dermatological consultant described the skin lesions as: "Toxic erythema probably of the erythema multiforme type, usually secondary to drugs or some systemic disease". The diagnosis of scleroderma was not particularly considered.

No papillœdema was noted, but one linear hæmorrhage was seen in the right fundus.

Several heart murmurs were noted, namely, an early diastolic at the apex, a systolic along the left border of the heart, and an early diastolic at the left sternal border. There was dullness to percussion at the lung bases, but no rales were heard. The abdomen was swollen but no masses were felt.

X-RAY AND LABORATORY DATA

Urinalysis.—On admission, specific gravity 1.016; acid reaction; protein, 160 mg. %; white cells, 5-8; red cells, 15-20; no casts.

Subsequent urinalyses gave a variable specific gravity, as high as 1.023 on February 7 and 1.024 on February 15. Reaction was neutral in one specimen on January 29; on other occasions, acid. Protein content varied from 130 mg. % on February 13 to 300 mg. % on February 8. Glucose was never present. Moderate numbers of red blood cells and white blood cells were present in all specimens. Granular casts were seen from time to time and both granular and hyaline casts in the last specimen.

Blood chemistry.—See Table I.

Hæmatology: January 28.—Red blood cell count, 5,100,000; Hb. value 16.4 g. %; white cell count 8500. Hæmatocrit 48%; differential count: polymorphonuclear leukocytes 75%; basophils 1%; lymphocytes 21%; monocytes 3%; sedimentation rate: 46 mm. in one hour (Wintrobe). L.E. cell search—negative (also negative on February 7). *February 12.*—Hb. value 14.42 g. %; hæmatocrit 49%; white cell count 6450; differential count: polymorphonuclear leukocytes 82%; lymphocytes 17%; monocytes 1%. *Stool.*—Negative for occult blood January 29, and twice on January 30. *Bacteriology.*—Urine culture, February 1: light growth of *E. coli.* Throat swab, January 30: normal respiratory flora. *Electrocardiogram,* January 28.—T wave low in limb leads. T negative in V2, slightly diphasic in V4, flat in V6. Tracing interpreted as showing non-specific myocardial changes. *Chest radiography,* January 28.—Bilateral pleural effusion, with patchy infiltration at the right base. Heart shadow not grossly enlarged. Some accentuation of vascular pattern throughout both lung fields. *Serology.*—Not performed.

COURSE IN HOSPITAL

The working diagnosis on admission was acute glomerulonephritis, with a possibility of systemic lupus erythematosus. As laboratory results came in, it became apparent that the patient was suffering from nephrotic syndrome as a phase of some chronic renal disease, which was presumed to be glomerulonephritis.

She was treated by conservative measures for the first week, in the hope that the nephrosis might clear spontaneously. Digitalis therapy, using digoxin, was instituted on January 28. Dietary salt was restricted; fluid intake was moderately restricted. On this regimen she remained œdematous, and measured output remained almost constantly below fluid intake. The blood pressure had fairly constant diastolic readings from 65 to 90, but the systolic varied from 160 to 205.

On February 4, various forms of more active therapy were instituted. She was given cortisone 300 mg. intramuscularly daily, and meralluride, 2 c.c. intramuscularly, this day and also on February 9 and 13. Penicillin, 400,000 units daily, was started. The protein supplied in her diet was increased to 100 g. daily, though it is doubtful how much of this she ate. On February 5, and again on February 8 and 10, 25 grams of concentrated human albumin was administered intravenously. This seemed to promote some slight increase in output.

On February 7 a peculiar mental change developed. She became disorientated, then withdrawn and tense; the house physician considered her to be in a schizoid, almost catatonic, state. Cortisone was discontinued, and she appeared normal the next morning, so that it was resumed at a reduced oral dose, along with propantheline bromide. On February 10 prednisone was substituted for cortisone, the dose again being relatively high, 15 mg. four times daily; this dosage was subsequently progressively reduced until it was discontinued on February 13.

About 8:30 on the morning of February 14, the patient began to have a series of grand mal seizures which lasted until 2:30 that afternoon, at which time she was given 0.06 g. phenobarbital sodium intramuscularly.

At 6:00 p.m. on February 14, her blood pressure fell, and she went into a coma from which she never recovered. Blood pressure fell from 190/70 to 120/70 mm. Hg, and then progressively down to 85/42 at 5:30

a.m. February 15. There was a temporary recovery on the morning of February 15, but after a further fall of blood pressure, it could only be maintained by administration of noradrenaline. Her temperature rose on February 15 to 103.4° F. (R). Cheyne-Stokes breathing developed during the night of February 15-16, and she died at 8:00 a.m. on February 16.

Except for a small amount of incontinence and 90 c.c. obtained by catheter, there was no urine output in the last 24 hours.

POST-MORTEM FINDINGS

At autopsy two hours after death, the body showed generalized œdema, most marked over the lower extremities. A sparse dry maculo-papular rash was scattered over the body. Some of the macules had petechial red centres. Enlarged soft discrete lymph nodes were palpable in the axillæ and groin areas. The peritoneal cavity contained 1000 c.c. of clear serous fluid. Pleural fibrous adhesions were present on both sides, being more marked on the left. The left pleural cavity contained 100 c.c. of fluid, the right 600 c.c. The pericardial sac was completely obliterated by fine fibrous adhesions.

The heart weighed 400 g. Mitral and aortic valve leaflets were slightly thickened and sclerotic, as were several mitral chordæ tendineæ. One aortic cusp was lightly calcified. The mitral valve was slightly stenosed. The myocardium was uniformly beefy red and firm, with hypertrophy of the left ventricle.

The lungs were heavy, poorly aerated, firm and lumpy, and the cut surfaces showed a corresponding patchy grey consolidation.

The left kidney weighed 230 mg., the right 200 mg. They were similar to one another with regular outlines but a tense appearance. On section the cut surfaces bulged. The capsules stripped readily and external surfaces were pale and "flea-bitten" by numerous red patches 1-3 mm. in diameter. The cortices were thick (0.8-1.0 cm.), pale, and mottled with red puncta. Medullæ, papillæ, calices, pelves and ureters showed no gross lesion. The urinary bladder was contracted and practically empty. The lining of the bladder was pale, smooth and glistening.

Two intramural fibroid tumours were seen in the uterus. A small hæmorrhagic corpus luteum was present in the right ovary.

The œsophagus was eroded superficially in its lower third; otherwise it was grossly normal.

Lymph nodes throughout were enlarged, discrete and uniformly soft. The cut surfaces were pale, moist and rather fleshy in appearance.

On miscroscopic examination the fundamental lesion was found to be a widely disseminated alteration of smaller arteries and arterioles with swelling and œdema-like pallor of the walls and narrowing of the lumen. Nuclei were increased in size and number and were distorted and irregular with some karyorrhexis.

The abnormal vessel walls had irregular staining characteristics and various evidences of degeneration such as splitting, incomplete lamination, fenestration, vacuolization, reticulation and myxoid œdema. There was no fibrinoid necrosis except in the brain; no inflammatory reaction and no aneurysmal dilatation, and only rare and questionable thrombosis. Except in the brain sections, there was no hæmorrhage. The vascular changes were strikingly manifest in the kidneys, brain, lymph nodes, spleen and heart; and less marked in the

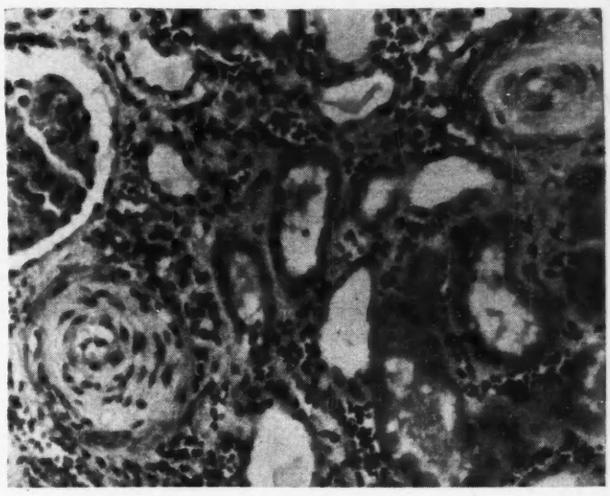


Fig. 1.—Scleroderma kidney with characteristic œdematous thickening and narrowing of small arteries (approx. ×150).

œsophagus, pancreas and liver. They were also presumed to be present in other locations including skeletal muscle, where distinction between post-mortem degeneration and true pathological alteration was difficult.

In the kidneys (Fig. 1), changes as noted above were seen in the subarcuate arteries and arterioles. There was also swelling of capillaries of the glomerular tufts with frequent small "wire-loop" effect and increased cellularity. The epithelial and endothelial nuclei were increased in size and number, with some irregular distortion and karyorrhexis. Syncytial epithelial hyperplasia was occasionally present. The glomerular tufts contained little blood. The capsular spaces were patent; they were either empty or else contained scant amorphous protein. The capsules were thin and well preserved. The convoluted tubules were dilated and contained abundant amorphous protein. A few hyaline casts and a rare granular cast were present. One tubule containing several polymorphonuclear leukocytes was found, and in a number of tubules there was regenerative epithelial proliferation. Interstitial tissue was not increased. Some œdema was present, and, rarely, local infiltration of inflammatory cells. These were chiefly lymphocytes, no polymorphonuclear leukocytes being identified.

Throughout the myocardium the typical vascular lesions were seen, with scattered areas of degeneration of muscle fibres. There were occasional minute stellate fibrous scars. No inflammatory cellular infiltration was present and no Aschoff bodies were found.

In the œsophagus there was localized acute exudative inflammatory reaction with superficial ulceration. This confused the histological picture but specific vascular lesions were present as described elsewhere, and, in addition, diffuse atrophy and fibrosis of the internal circular muscular coat.

The skin showed mild swelling of dermal collagen bundles and light infiltration of lymphocytes about adnexa and vessels. There were only slight vascular changes of a questionable character. The subcutaneous tissue showed no lesion.

In the lungs extensive bronchopneumonia was present, with leukocytic exudate but with moderate fibrinoid and large mononuclear cell components. Specific vascular changes were not evident.

Examination of Brain

The brain was large, weighing 1520 g. before fixation, and the convolutions were flattened against the dura. There was no significant degree of temporal lobe or cerebellar herniation. However, the mammillary bodies were displaced downwards, indicating some degree of downward movement of the brain stem, probably not enough to produce significant upper brain-stem compression. The major arteries and veins were not abnormal, nor were the meninges.

In the coronal sections of the cerebrum small vessels appeared unduly prominent. A small petechial hæmorrhage was recognized in the white matter of the left parietal lobe, and a small pale softening of irregular outline in the left thalamus. On sectioning the brain stem, another similar pale infarct was seen in the right restiform body. The ventricles were small.

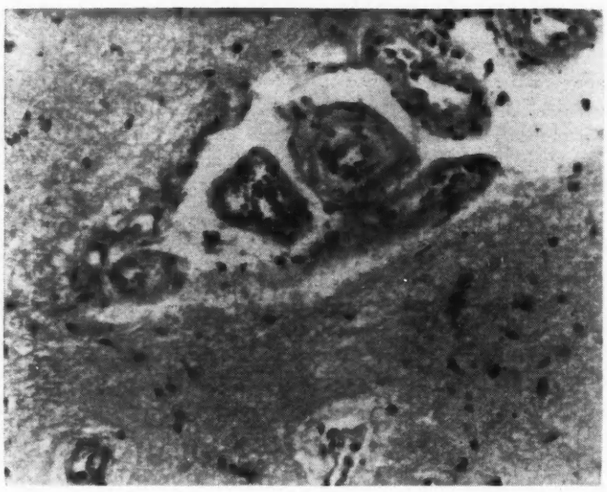


Fig. 2.—Scleroderma brain; œdematous stenosis of small arteries of meninges and cortex (approx. ×150).

The most striking histological change was found in the arterioles and small arteries of a diameter of approximately 50 to 200 microns (Fig. 2). Many of these vessels had a loose mucinous fibroblastic thickening of the intima, sometimes so severe as to occlude completely the lumen of the smallest vessels. Thrombi were present within the lumen of some of these vessels. This change was not recognized in the cerebellum or ependyma, and varied greatly in intensity in the meninges, cerebrum, basal ganglia and brain stem. In some areas groups of small arterioles, approximately 50 microns in diameter, showed smudgy necrosis, without any accompanying cellular reaction. A few of these vessels appeared to have leaked, and small clumps of red blood corpuscles were seen close to them. Scattered petechial hæmorrhages were found in some sections of the cortex; these clearly arose from small veins and appeared agonal. The veins were congested, but no other change was present, and the larger arteries appeared essentially normal. About two dozen small pale infarcts were found scattered through the cortex, white matter and brain stem, without any cellular reaction, and often contained surviving plump astrocytes within them. One infarct was seen with a considerable microglial and polymorphonuclear leukocytic reaction surrounding it. In addition, in other areas small groups of swollen nerve cells with central chromatolysis and ectopic large pale nuclei were present. The histological evidence of ischæmia was relatively trivial in comparison with the severe cerebral illness and the extent of the vascular change.

DISCUSSION

Renal Scleroderma

In the past 20 years scleroderma involving the kidneys has been described in several reports.[1-12] Most of the earlier cases, some of which will not be referred to here, have been summarized by Moore and Sheehan.[12] In recent years there have been some comprehensive reviews of the subject, variable numbers of cases being reported.[12-14]

The early impression was that the condition was a rarity, but more recently Piper and Helwig[15] have reported that in five out of 31 cases death was due to renal failure. Fisher and Rodnan[14] found renal involvement in nine of 11 cases studied. Leinwand, Duryee and Richter[16] state that all of their patients who came to autopsy had some involvement of the kidney. This was apparently appreciated by Osler who, in his text-book, stated that patients with scleroderma "are apt to succumb to pulmonary complaints or to nephritis".

In the course of these observations an appreciation of the morphological appearance of a "scleroderma kidney" has developed. Grossly, the cut surface contains nodular elevations with an appearance like subacute pyelonephritis. There are scattered red, congested or hæmorrhagic areas and occasional infarcts. The microscopic changes have been set down systematically by Calvert and Owen,[8] who enlarged upon the earlier description of Moore and Sheehan.[12] With some further modifications, the description is as follows:

1. In the intralobular arteries, proximally, there is a concentric mucoid intimal thickening with gross reduction in the lumen. Talbott *et al.*[1] speak of this thickening as being due to "a sparsely nucleated, patchy basophilic mucinous material which had the appearance of Wharton's jelly".

2. In the intralobular arteries, peripherally, fibrinoid necrosis of media and intima is present. This necrosis is also seen in some of the afferent arterioles.

3. Renal cortical ischæmic lesions develop, including fresh to old infarcts.

4. Areas of tubular degeneration and intertubular fibrosis are also seen. The convoluted tubules particularly are affected; the collecting tubules are relatively free.[14]

5. Glomerular changes are extremely variable. Typically the fibrinoid necrosis involves the walls of the afferent arterioles and glomerular loops.[13] Frequently, as in this case, occasional "wire loop" lesions, usually considered typical of lupus erythematosus, have been noted.[2, 10]

This overlap in the pathology of renal scleroderma and other related conditions has also extended in other directions. A similarity to periarteritis nodosa has been noted by some,[3, 4] and still others

have observed similarity to malignant hypertension.[14, 17, 18, 21]

Along with the accepted pathological appearance, a reasonably uniform clinical course has become apparent. Early in the course of a case of scleroderma, symptoms and signs suggesting renal involvement may be scanty or absent. It now appears that in the later stages hypertension is a common development,[13, 14] though previously it was considered uncommon.[12] The hypertension is rapidly followed by retinopathy, cardiac failure, convulsions, profound oliguria and uræmia. The progression of the disease from the appearance of hypertension to death is usually so rapid that there is little time for clinical evidence of renal disease to become fully apparent.

There have been frequent variations from this typical clinical course. In some cases renal involvement, along with skin lesions, was the first thing observed.[15] In two cases reported by Piper and Helwig,[15] as in the present case, scleroderma was not anticipated at all from the clinical course, but renal involvement was found at autopsy.

Recently several attempts have been made to deduce the natural history of the disease from the appearance of the various lesions. Moore and Sheehan[12] felt that the initial lesion was the dilatation of segments of the intralobular arteries and associated thickening of the intima. This seems to develop only a few weeks before death and leads to ischæmic atrophy of large portions of the renal cortex. The subsequent lesion is the fibrinoid necrosis of the distal intralobular arteries and afferent arterioles. This shows no healing at autopsy and probably develops only a few days before death. The acute ischæmic lesions in the related parenchyma also develop in the last few days of life and lead to the final deterioration of renal function and death.

Rodnan, Schreiner and Black[13] and Sokoloff[17] postulate that the renal lesions are an end result of localized vasomotor activity of the renal vessels, similar to that of Raynaud's phenomenon in the digital vessels. This abnormal state of vasoconstriction and dilatation leads to hypertension and the terminal fibrinoid necrosis. As there is a marked similarity between the renal lesions of scleroderma and those of malignant nephrosclerosis, it is possible, on the other hand, that the hypertension might also be the cause of the final stages. Obviously renal biopsies in diagnosed cases of scleroderma will be of value in clarifying the time-relationship of the pathological processes.

In several case reports and articles[5, 18-21] comment has been made upon an apparent relationship between steroid therapy for scleroderma and the development of the clinical signs of renal involvement leading to death; and considerable concern has been expressed about the possible harmful effects of steroids. It must be borne in mind that the typical hypertensive crisis has occurred in many patients, independent of such therapy. As yet no definite conclusions can be drawn as to whether steroids may induce these renal changes or merely accelerate a process which has already begun. If there is any connection between steroids and the development of renal involvement, possibly prednisone and further refined steroids may be less prone to produce such effects.

The case herewith presented differs in several respects from the typical one of renal scleroderma. First, although there were dermatitis and minimal vascular changes in the skin at autopsy, there was no characteristic sclerodermatous affection of the skin itself. Secondly, unlike almost all other reported renal cases, this one had a clinical picture in which symptoms and signs of renal disease were so prominent that scleroderma was not suspected *ante mortem*, though lupus erythematosus was considered in the differential diagnosis. Finally, in following a course like that of nephrotic syndrome, this case seems to have been almost unique. In only a few previous cases[3, 5, 7, 13] were œdema and severe albuminuria pronounced features; to a certain extent these cases resembled the present one. In the final stages this patient ran the typical course of hypertension, renal failure, convulsions and death, though neither the blood pressure nor blood urea level was excessively abnormal. It is probable that the neurological lesions also entered into the production of the convulsions.

In this case, as in those referred to above, it is possible that the fatal process was accelerated by steroid therapy.

Cerebral Involvement

There are very few detailed descriptions of clinical manifestations of involvement of the central nervous system by scleroderma, and only an occasional pathological description. It is doubtful that the condition of facial hemiatrophy, occasionally observed by the dermatologists to be associated with morphœa, is due to true scleroderma; but in 1922, Osborne[22] reviewed the literature of this condition and referred to recorded cases back to 1886; the evidence in the literature and in his own cases suggested involvement of the central nervous system.

Some other isolated neurological and neuropathological descriptions have been recorded.[9] Richter[23] described a patient with generalized scleroderma in whom the most prominent feature was peripheral neuropathy.

Earlier, convulsions in the course of scleroderma were considered rare and a possible indication of neurological involvement. Now, as was discussed in the previous section, convulsions have been reported frequently in the later stages of the renal cases, and are possibly related to the hypertension and uræmia.

In the present case the brain showed evidence of disseminated ischæmic encephalopathy with many minute infarcts which were mostly too recent to have developed a cellular reaction, and a generalized swelling of the brain, secondary to this

ischæmia. The cerebral illness began quite suddenly with a psychotic episode nine days before death, followed by a series of major seizures and coma for the last two days of life. The clinical course and pathological appearance were very similar to other forms of disseminated patchy, ischæmic encephalopathy in which multitudes of small arteries or arterioles are narrowed or occluded. The uncommon condition of severe hypertensive arteriolar sclerosis produces the same clinical and pathological course but at a slower pace, and a patient with thrombotic microangiitis, whose brain was examined in this laboratory, had an almost identical pathological picture. The clinical and pathological features of the much commoner encephalopathy of systemic lupus erythematosus are identical except for the different nature of the arterial and arteriolar lesions.[24] In our patient the narrowing of the minute vessels was caused by scleroderma; the venous hæmorrhages were considered agonal and of no significance. It is to be noted that most of the infarcts were recent and were too small and too few to account for the severity of the cerebral illness. This is the common finding in the more acute forms of disseminated ischæmic encephalopathy. It is probable that the blood supply to large regions of the brain had been reduced by the vascular occlusions to a point where the brain could still survive but no longer function. It is only where the disease was particularly intense that the blood supply was reduced to a point where infarction occurred. This patient had only mild uræmia, and the hypertension never reached levels commonly associated with hypertensive encephalopathy. Byrom[25] produced very convincing evidence that the disseminated ischæmic encephalopathy of this disease was a product of intense arteriolar spasm in reaction to extreme elevation of blood pressure. It is not unlikely that intense arterial and arteriolar spasm may develop in response to a much lower level of hypertension if the vessels are already damaged by scleroderma or systemic lupus erythematosus.

SUMMARY

A case of generalized scleroderma (progressive systemic sclerosis) is presented with autopsy findings. Clinical and pathological studies were of particular interest in reference to kidneys and brain. The kidneys were typical of scleroderma at autopsy, but the clinical course was unusual in that it resembled that of nephrotic syndrome until the final stages. Cerebral symptoms were attributed to ischæmia secondary to the sclerodermatous changes in the cerebral arteries and arterioles where the disease process was more intense than elsewhere in the body. The patient was treated with cortisone and prednisone, which may possibly have influenced the course of the disease. The literature on renal and cerebral scleroderma is reviewed.

REFERENCES

1. TALBOTT, J. H. *et al.*: *Arch. Int. Med.*, 63: 476, 1939.
2. MATHISEN, A. K. AND PALMER, J. D.: *Am. Heart J.*, 33: 366, 1947.
3. PLATT, R. AND DAVSON, J.: *Quart. J. Med.*, 19: 33, 1950.
4. SWARM, R. L. AND GERMUTH, F. G. JR.: *Am. J. Path.*, 29: 577, 1953. (abstract)
5. Clinico-pathologic conference (Washington University): *Am. J. Med.*, 14: 231, 1953.
6. BARTELS, E. D., CHRISTENSEN, L. R. AND OHLSEN, A. S.: *Acta path. et microbiol. scandinav.*, (supp. 105): 174, 1955.
7. HANNIGAN, C. A., HANNIGAN, M. H. AND SCOTT, E. L.: *Am. J. Med.*, 20: 793, 1956.
8. CALVERT, R. J. AND OWEN, T. K.: *Lancet*, 2: 19, 1956.
9. Case Records of the Massachussetts General Hospital, Case No. 42211: *New England J. Med.*, 254: 998, 1956.
10. Case Records of the Massachussetts General Hospital, Case No. 43341: *Ibid.*, 257: 378, 1957.
11. FRED, H. L. AND RAMBO, O. N.: *A.M.A. Arch. Int. Med.*, 100: 813, 1957.
12. MOORE, H. C. AND SHEEHAN, H. L.: *Lancet*, 1: 68, 1952.
13. RODNAN, G. P., SCHREINER, G. E. AND BLACK, R. L.: *Am. J. Med.*, 23: 445, 1957.
14. FISHER, E. R. AND RODNAN, G. P.: *A.M.A. Arch. Path.*, 65: 29, 1958.
15. PIPER, W. N. AND HELWIG, E. B.: *A.M.A. Arch. Dermat.*, 72: 535, 1955.
16. LEINWAND, I., DURYEE, A. W. AND RICHTER, M. N.: *Ann. Int. Med.*, 41: 1003, 1954.
17. SOKOLOFF, L.: *Bull. New York Acad. Med.*, 32: 760, 1956.
18. LUNSETH, J. H., BAKER, L. A. AND SHIFRIN, A.: *A.M.A. Arch. Int. Med.*, 88: 783, 1951.
19. SHARNOFF, J. G., CARIDEO, H. L. AND STEIN, I. D.: *J. A. M. A.*, 145: 1230, 1951.
20. O'LEARY, P. A. AND ERICKSON, J. G.: *Ibid.*, 152: 1695, 1953.
21. BAGNALL, A. W. AND ROBINSON, H. S.: *Clin. Res. Proc.*, 2: 145, 1954.
22. OSBORNE, E. D.: *Arch. Dermat. & Syph.*, 6: 27, 1922.
23. RICHTER, R. B.: *J. Neuropath. & Exper. Neurol.*, 13: 168, 1954.
24. DALY, D.: *J. Nerv. & Ment. Dis.*, 102: 461, 1945.
25. BYROM, F. B.: *Lancet*, 2: 201, 1954.

REITER'S SYNDROME OCCURRING IN THE FEMALE*

REPORT OF A CASE SHOWING THE COMPLETE TRIAD AND OTHER FEATURES

H. A. WARNER, M.D., J. R. MARTIN, M.D., F.R.C.P.[C.] and DOUGLAS G. CAMERON, M.D., F.R.C.P.[C.], *Montreal*

REITER'S syndrome is rare in females. If the exact criteria of urethritis, conjunctivitis and arthritis are followed only four cases reported in the literature would qualify.[1-3] Other cases have been described but they had only two features of the triad, or gonorrhœa, or the protocol contained no direct mention of urethritis as distinct from vaginal discharge.[2-5] The patient reported here is interesting since she showed the three diagnostic features, and in addition, other mucocutaneous lesions.

A 33-year-old unmarried, white, school teacher came to the outpatient department of the Montreal General Hospital on September 28, 1958, complaining of profuse vaginal and urethral discharge, burning urination and painful inflamed eyes.

The patient stated that she had been subject to recurrent attacks of allergic non-purulent conjunctivitis each autumn for the past seven years. Six weeks previously she had had a single sexual exposure. This was followed ten days later by a bout of diarrhœa lasting one day. As this was receding she developed urethral irritation and vaginal discharge, both of which persisted. Two weeks later her eyes began to smart, bright lights bothered her and her eyelids stuck together in the mornings. Her companion stated that he had not had urethritis at the time of sexual contact, and subsequently he did not develop any symptoms.

*From the Department of Medicine, Montreal General Hospital.

A physician prescribed penicillin tablets for one week, but since none of her symptoms improved she decided to seek further advice.

On examination vascular conjunctivitis with scanty white exudate was noted in both eyes. Profuse vaginal discharge was present. The vulva and urethral orifice were erythematous, and purulent material was expressible from the urethra. Bartholin's glands were not inflamed and the rest of the pelvic examination was negative. Smear and culture of the vaginal discharge did not reveal gonococci or other pathogenic organisms. A light growth of micrococci was obtained from the conjunctival exudate. She received 400,000 units of penicillin and one gram of streptomycin on three successive days, as well as neosporin and cortisone ophthalmic ointment. During the ensuing week the right ankle became painful and swollen, and small ulcers developed in her mouth. Since her other symptoms had not improved, she was admitted on October 11 for further investigation.

PHYSICAL EXAMINATION

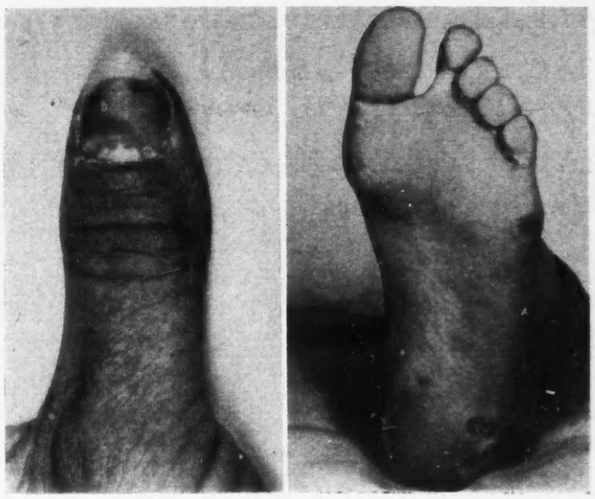
The patient was normotensive, with a pulse rate of 85 per minute. Numerous shallow aphthous ulcers were noted on the soft palate and fauces. No vesicles were seen. A "paronychia-like" lesion was found under the lunula of the right thumb nail (Fig. 1a). This consisted of material which had the appearance and consistency of cottage cheese. Her right ankle was swollen, red and tender, with limitation of movement. Several discrete hemispherical lesions consisting of thickened skin were observed on the soles of the feet (Fig. 1b). The conjunctivitis and the vaginal and urethral discharges were still present. Examination of the chest, heart and abdomen did not reveal anything noteworthy. There was no lymphadenopathy.

INVESTIGATIONS

Hæmatocrit value was 43%, white cell count 12,800 per c.mm., with 74% neutrophils, 6% eosinophils, 1% basophils, 16% lymphocytes and 3% monocytes. The erythrocyte sedimentation rate was 31 mm. in one hour (Wintrobe). The urine showed a trace of protein and gross pyuria. Roentgenograms of the chest and hands were normal. Repeated roentgenograms of the ankles and feet revealed demineralization and an irregular resorption and proliferation of the cortical bone in the region of the right ankle. Two electrocardiograms, the blood Wassermann test, Brucella agglutination values, the Widal test, serum uric acid, plasma protein and blood urea nitrogen levels, the anti-streptolysin titre and cephalin-cholesterol flocculation value were all normal. On several occasions cultures of the urethral and vaginal discharges had a moderate growth of *E. coli*. The right ankle was aspirated. Many lymphocytes were present in the synovial fluid but no tubercle bacilli or other organisms were found.

HOSPITAL COURSE

The patient was afebrile throughout her stay in hospital. Shortly after her admission the left shoulder and the dorsum of the left foot became painful, but these symptoms disappeared after a few days. She was given 600,000 units of procaine penicillin twice daily for two weeks, and the ophthalmic ointment was continued. The conjunctivitis and stomal lesions improved slowly and the vaginal-urethral discharge diminished gradually. The nail was elevated by the "paronychia-like" lesion. A similar condition appeared under several other finger nails, the great-toe nails and other toe nails, causing them to drop off. They were eventually replaced by new nails. Since the right ankle failed to respond to this regimen, she was given an infusion of 30 units of adrenocorticotrophin over a period of eight hours. A day later she was started on 20 units of the long-acting hormone preparation daily. Within 12 hours pain disappeared from the ankle, and three days later she was able to walk without discomfort.



(a) (b)

Fig. 1.—(a) "Paronychia-like" lesions. (b) Cutaneous lesions on the sole.

One week later she was discharged and has been followed up in the arthritis clinic. Prednisone was substituted for adrenocorticotrophin. At the time of writing (October 1959) she had not received any medication for two months. Apart from an occasional ache in the right ankle, she is free of symptoms.

SUMMARY

A case of Reiter's syndrome, possibly of venereal origin, displaying the complete triad of urethritis, conjunctivitis and arthritis and occurring in a young woman has been presented. She had eosinophilia, keratodermia blennorrhagicum, mucocutaneous lesions, diarrhœa and subungual accumulations of keratotic material with temporary loss of the affected nails. There was, as well, a history of recurrent allergic non-suppurative conjunctivitis, which has been described as a part of the natural history of the syndrome.[6] Except for transient involvement of the left shoulder, the arthritis was present only in the right ankle. Penicillin therapy did not seem to influence the progress of the conjunctivitis, stomal lesions or the urethral-vaginal discharge, although these subsided slowly during a course of treatment with the antibiotic. The arthritis responded promptly to adrenocorticotrophin, and complete remission was subsequently maintained with prednisone. This was later withdrawn without recurrence of her symptoms.

REFERENCES

1. RINKOFF, S.: *J. A. M. A.*, **148**: 740, 1952.
2. REFVEM, O.: *Acta rheumat. scandinav.*, **3**: 282, 1957.
3. ZEWI, M.: *Acta ophth.*, **25**: 47, 1947.
4. CLARK, C. J. M.: *Ann. Rheumat. Dis.*, **10**: 80, 1951.
5. OATES, J. K. AND CSONKA, G. W.: *Ibid.*, **18**: 37, 1959.
6. SMYTH, C. J. *et al.*: *Ann. Int. Med.*, **50**: 642, 1959.

Canad. M. A. J.
April 23, 1960, vol. 82

THE CANADIAN MEDICAL ASSOCIATION
JOURNAL
LE JOURNAL DE
L'ASSOCIATION MÉDICALE CANADIENNE

published weekly by
THE CANADIAN MEDICAL ASSOCIATION
Acting Editor: H. E. MACDERMOT, M.D., F.R.C.P.[C.]
Managing Editor: T. C. ROUTLEY, M.D., F.R.C.P.[C.]
Assistant Editors: M. R. DUFRESNE, M.D.
GORDON T. DICKINSON, M.D.
Editorial Offices: 150 ST. GEORGE ST., TORONTO
(Information regarding contributions and advertising will be found on the second page following the reading material.)

HOW SHALL WE RESUSCITATE?

It is encouraging that there should be continued discussion on the subject of resuscitation, including of course the methods to be employed: "the tree of life is never quiet", and its movements cause constant shifts in the emphasis on what is best to be done to restore life which has been accidentally suspended.

Since the field of emergency is infinite in variety, there will always be various methods of resuscitation. When an anæsthetist, for example, deals with failure of respiration on the operating table he automatically turns to accepted procedures with up-to-date equipment. But the layman (or indeed even the same anæsthetist) who has to resuscitate a case of apparent drowning at a distant lake, cannot proceed with such certainty that he is choosing the best possible method. In other words, methods must vary with circumstances. The important matter is knowing which method to employ and deciding as quickly as may be.

Among the many methods of resuscitation which history reveals with her usual impassivity, that of direct or mouth-to-mouth respiration is the oldest, and it produces the largest volume of tidal air exchange. Yet only recently has it been put back amongst the recommended methods of resuscitation. Its æsthetic disadvantages are obvious but it is well to remember its value, especially in children. The numerous methods of manual respiration, Silvester, Schafer, Holger-Nielsen, Eve rocking, are all well known and are thoroughly taught to large numbers of first-aid men. Concentration on one or two of these accepted methods is perhaps best.

The numerous forms of mechanical inhalators and resuscitators that are being put forward have their place, but should only be used by those who understand their disadvantages.

Editorial Comments

BASIC CONSIDERATIONS IN MENTAL RETARDATION*

This is the title of a document formulated by the committee on mental retardation of the Group for the Advancement of Psychiatry. An accompanying press release states that it represents the point of view of 250 psychiatrists in the United States and Canada. An appendix to the report, however, lists as members approximately 185 psychiatrists, of whom six are in Canada. The stated aims of the Group are: (1) to collect and appraise significant data in the field of psychiatry, mental health and human relations; (2) to re-evaluate old concepts and to develop and test new ones; and (3) to apply the knowledge thus obtained for the promotion of mental health in good human relations.

The present report would appear to be largely concerned with the second objective. Perhaps the key note is struck in the introduction, where the statement appears, "While it is self-evident that mental retardation should be of major concern to psychiatry, psychiatrists know little about it and often show, at best, minimal interest in the problem." It is the aim of the report to draw attention to this state of affairs, to provide guidance on the scope of mental retardation, and to suggest ways whereby psychiatrists may enter more fully into this neglected part of their heritage.

The authors make it clear that in the United States the control of state mental-deficiency institutions does not follow the same pattern as in Canada. In this country provincial institutions are administered by qualified psychiatrists. In the United States, on the other hand, more than a third of state institutions are under entirely non-medical administration, and of the remainder a third are administered by physicians unqualified in psychiatry. From this it follows that a good deal of the report is more applicable to American than to Canadian conditions.

The writers stress the need for adequate consideration of all facets of mental retardation before arriving at a diagnosis. Every case should be studied from a psychological, cultural, social and somatic angle. Consideration of the psychological component is seen to extend beyond ascertainment of an intelligence quotient to take in the whole wide range of emotional life, while the importance of cultural and social factors is certainly not underestimated. The report observes that residential admission of the mildly retarded is usually the result of superimposed emotional disturbance in the child or family. The difficulties of differential diagnosis in particular are cited as an argument for active psychiatric participation. With perfect justification the authors point out that it is not always possible to undertake an exact classification of deviant children into clear-cut categories like mentally retarded, psychotic, neurotic, and those with character problems. An illustrative example is that of early infantile autism where a fundamentally psychotic process can produce a picture

*Basic Considerations in Mental Retardation: A Preliminary Report, Report No. 43, Committee on Mental Retardation, Publication Office, Group for The Advancement of Psychiatry, 104 East 25th St., New York 10, N.Y., 25 pp., 40c.

with a close superficial resemblance to mental retardation.

Note is taken of the steady development within the community of special public school programs for both educable and trainable groups, and this is seen to be paralleled by a corresponding change in orientation within state institutions away from the merely custodial towards a growing program of return to the community. Nevertheless, the report envisages the provision of additional facilities in the form of psychiatric centres for children, sufficiently complex to include in-patient, out-patient and day hospital services. Serving primarily the need for comprehensive differential diagnosis, such centres, providing diversified medical and other therapeutic skills for all groups of psychiatrically deviant children, would, it is argued, give the mentally retarded group maximum opportunity to overcome their handicap.

This scheme, the major recommendation of the report, calls to mind the excellent demonstration community centres planned for New York State, the objectives of which are to provide not only comprehensive differential diagnosis but also adequate counselling service for parents of retardates, as well as far-reaching facilities for retardates themselves, mild and severe, young and old, whether living in the community, on their way to state institutions, or returning thence to the community. Apart from differential diagnosis, however, this type of centre limits itself exclusively to facilities for the mentally retarded. Still, if a structure is proposed with the degree of elaboration indicated in the current report, and if it is genuinely intended to serve the needs of defectives, the example set by New York State would appear to be a not unworthy prototype. A similar establishment, this time Canadian, is the research centre which is shortly to open in London, Ontario. This admirable project is destined to furnish out-patient facilities, short-term training for retardates, counselling for parents, and diagnostic and screening programs to evaluate degrees of retardation. Another possible method of meeting community needs, which seems to have eluded mention in the report, might be simply to improve facilities in state institutions so as to attract, train, and retain staff qualified in differential diagnosis and other aspects of mental retardation.

ROBERT GIBSON

INTRATHECAL PHENOL FOR SPASMS AND SPASTICITY

Two of the great nuisances associated with a total paralysis of the lower limbs are spasticity and recurring spasms. The patient may be made miserable by the sudden onset of spasms, triggered by such stimuli as noise or an attempt to move him, and the spasticity and spasms may be accompanied by a severe aching pain or even spasmodic bouts of agony. In addition the sensation of muscular tension which these patients frequently complain of tires them out, while the spasms may be accompanied by bladder incontinence. If such a spasmodic and spastic condition can be converted into a flaccid paralysis of the lower limbs, the patient's nursing will be much easier, he will be more willing to move himself about, his bladder will no longer have a tendency to empty with each spasm and can be trained to empty automatically, his bedsores will slowly heal and there is a chance to correct deformity.

Various attempts have been made to convert spastic into flaccid paralysis, of which the most obvious was the division of anterior spinal roots, a long and difficult operation which can scarcely be undertaken on patients in poor health. The alternative would seem to be the destruction of the anterior spinal roots by a chemical substance, and for this purpose alcohol injected intrathecally has been used, but was not found very satisfactory. Other antispastic drugs have been tried and proved disappointing; these include curare, mephenesin, chlorpromazine, zoxazolamine and meprobamate. The presence of side effects and a great variability in general effect have precluded their widespread use.

Two papers from London, England (*Lancet*, 2: 1099 and 1102, 1959) report some satisfactory studies of the use of intrathecal injections of phenol to relieve spasm and spasticity. The authors, Nathan, and Kelly and Gautier-Smith respectively, have both tried using phenol in two different solvents, glycerol and Myodil (ethyl iodophenylundecylate). Various concentrations were used for experimental work on cats, and it is suggested that a suitable concentration in glycerol is from 5% to 20%. In Myodil the two authors used concentrations varying between 25% and 5%. Nathan suggests that the amount of the solution injected is determined by the number of roots it is designed to affect, although there is some variability in results. Usually 1 ml. of a 25% solution in Myodil affects seven to eight roots, while 0.5 ml. affects two to three roots. No seriously untoward reactions have yet been encountered when the roots of nerves to the lower limbs were being injected.

Kelly and Gautier-Smith mention a few complications. Two patients had a headache after injection but it cleared within 24 hours, while the pain which developed in a leg in three cases also cleared in a few days. Bladder disturbance occurred occasionally, and some transient numbness of the leg affected many patients, though it was permanent only in nine. Two patients had a fairly severe reaction about 15 minutes after injection of the phenol solution in Myodil, but recovered rapidly with an antihistamine injection.

One paper describes the treatment of 25 patients, 18 of whom had disseminated sclerosis, while the other authors treated 32 patients, of whom 20 had disseminated sclerosis. The other patients had a variety of lesions such as extradural abscess, cerebral hæmorrhage, amyotrophic lateral sclerosis, or tumour. Results were in general very good; bed-ridden patients were able to sit up in a wheel chair, and some voluntary movement which had been prevented by spasticity now became apparent. In 16 out of 25 patients who had had severe spasm, the spasm was abolished while in seven others it was much reduced and became painless.

It is pointed out that regeneration of fibres of anterior roots after these injections is certainly

Canad. M. A. J.
April 23, 1960, vol. 82

possible. In some cases spasticity and spasms recurred, possibly because of regeneration, but in one series of 25 patients only one had a return of spasms severe enough to warrant another injection a year after the first. In the other series four patients have had a recurrence of less severe spasm and these have all responded to reinjection.

The authors of both papers point out that further work is in progress but that experience so far indicates that spasms can be stopped and spasticity reduced in this way. At the present moment the treatment has been confined to bed-ridden patients; in the near future ambulant patients are also to be treated.

BREAKING THE BARRIER CREAM BUBBLE

"Well, well, sir, your credentials?"—Voltaire

F. R. Bettley, in a recent lecture,[1] has spoken of the many aspects of the use and abuse of the barrier creams. In preventing any sensitization dermatitis, the only sure safeguard is avoidance of contact, whether it be by direct contact or indirectly by benches, door handles and machinery. The idea of using barrier creams was suggested 45 years ago. In 1956 the British Ministry of Labour gave its official blessing to these creams.

"In theory the conception of a barrier is excellent; it is to form an invisible, impalpable, inodorous and innocuous layer on the skin, flexible and unbreakable, which will allow perspiration and evaporation to take place from the skin, but which is above all impermeable—from the outside . . . To believe in a substance so nearly bordering on the miraculous requires either a naïve credulity or the most conclusive scientific evidence. The latter certainly does not exist."[1]

In vitro tests are highly artificial and take no account of temperature, friction or sweating. Immersing the hands, previously smeared with a cream, into caustic solutions "does not warrant serious consideration. [These tests] are more akin to parlour tricks and are designed to sell the products rather than test them." Bettley maintains that there is no good evidence that barrier creams make cleansing of the skin easier. The problem of cleansing the skin is a complex one and depends on the amount and nature of the dirt to be removed. This might lead to follicular blockage, sweat duct occlusion and irritation of the skin surface. In evaluating *in vitro* tests many factors have to be considered. Very frequently the introduction of barrier creams is associated wth improvements in cleansing facilities, working techniques, extra awareness and extra care by the worker, and increased sympathetic medical supervision. It is very difficult to tell whether the improvement is due to the cream or to the other means of prevention which are being used at the same time. The use of barrier creams about colostomy openings may be helpful—but here the cream can be applied thickly, there is no appreciable movement, and there is no rubbing off. Also, for many years it has been shown that a thick layer of simple paste will do equally well in such conditions. Barrier creams may contain up to 12% hard soap. This is a primary irritant and may cause a dermatitis itself or, more important, it may increase the chance of the development of a true sensitization dermatitis—exactly the opposite of what it was supposed to do! The same results may develop from the base.

Bettley ends his lecture by making two pleas: one is for a carefully designed, statistically significant experiment to determine the actual value of barrier creams, and the other is for the release by the manufacturers of the formulæ of proprietary barrier creams. Bettley does not claim that barrier creams are useless; he uses the Scottish verdict, "not proven".

ROBERT JACKSON

REFERENCE

1. Malcolm Morris Memorial Lecture held at the Wright-Fleming Institute in London, England, on December 10, 1959.

DRUG TREATMENT OF ANGINA PECTORIS

The latest report on "successful" treatment of angina pectoris comes from Manchester (England). MacKinnon, Anderson and Howitt[1] report a controlled "double-blind" trial of "cavodil", a hydrazine analogue of amphetamine which was made in 28 patients with angina pectoris. They found that improvement occurred in 85% of patients on cavodil as compared with 48% on placebo. Their findings were encouraging enough to suggest to them that it may become a useful drug in the management of anginal pain. In the same issue of the *British Medical Journal*, an editorial reviews the various drugs that have been used in angina pectoris and the disappointment which inevitably followed the initial enthusiasm with the drugs, starting with the xanthines and going on to long-acting nitrate and more recently to slow-release nitroglycerin.[2]

The editor quite rightly points to the often forgotten fact that symptomatic relief does not affect the underlying coronary arterial disease, which is after all the most important concern to the doctor.

What is worthy of note in this long history of initial success and subsequent failure of one or the other drugs in angina pectoris (and for that matter in many other painful disorders) is that even the "double-blind" method has not been absolutely foolproof. It is obvious by now that repeated "double-blind" trials have to be carried out in order to ensure that the initial good results can be reproduced at will.

This need not discourage the individual physician who has found one or the other drug to work well on his own patients with angina. One has to be honest enough with oneself to admit that the good results may be due to the placebo effect of the drug plus the positive approach of physician and patient to the treatment.

W. GROBIN

REFERENCES

1. MACKINNON, J., ANDERSON, D. E. AND HOWITT, G.: *Brit. M. J.*, 1: 243, 1960.
2. EDITORIAL: *Ibid.*, 1: 257, 1960.

Medical News in brief

INFECTION WITH TUBERCLE BACILLI INITIALLY RESISTANT TO STREPTOMYCIN OR TO ISONIAZID

In a study of 687 strains of tubercle bacilli from children with primary tuberculosis, 398 were isolated from patients who had not been treated with streptomycin, and 18 of these were resistant to streptomycin. There has been a lag period of three years between the time when streptomycin became available in France and the appearance of the first cases of initial resistance to streptomycin in untreated patients. In 1952, the incidence of infection with streptomycin-resistant tubercle bacilli in this hospital service increased to one of 33. Since then and coincidentally with the introduction of isoniazid, this increase has stopped, and the overall incidence is about 5%.

Since 1955, there have been three cases of children infected with streptomycin-resistant tubercle bacilli whose infection had been contracted from untreated mothers. Although precise information is lacking about the history of the mothers and the susceptibility of the tubercle bacilli from their sputum, it should be noted that all three were young and had very likely been contaminated at a period when streptomycin-resistant organisms were frequently encountered.

Infection with strains highly resistant to isoniazid and of decreased pathogenicity for guinea-pigs has been observed by several writers. In the present series, a lag phase has been seen for isoniazid, as with streptomycin: in 1957, for the first time, four isoniazid-resistant (of a degree that is clinically significant) strains were found in untreated patients.

Infection of non-allergic children with strains of tubercle bacilli resistant to drugs available at present is a fact, the clinical significance of which is now well proved. This danger should not be disregarded. It does not become evident in the first years after a new drug becomes available, as its occurrence is postponed and limited by the fact that untreated patients remain the main source of contact. The importance of this hazard makes it as necessary as ever to use multiple-drug therapy and to isolate patients who continue to discharge tubercle bacilli in the sputum. — R. Debré *et al.*, *Am. Rev. Respiratory Dis.*, 80: 326, 1959.

SURGERY IN ATHEROSCLEROSIS

Professor Charles Rob, M.C., F.R.C.S., in a Symposium on Atherosclerosis before the Royal Society of Medicine (*Proc. Roy. Soc. Med.*, 1: 38, 1960) points out that the surgeon can treat a patient with arterial insufficiency in only one of the following ways: arterial reconstruction designed to restore normal or nearly normal blood flow; an operation to increase the efficiency of the collateral circulation; an operation to reduce symptoms by limiting the function of ischæmic tissues; and an amputation or excision of ischæmic tissues. Some patients with atherosclerosis develop arterial aneurysms and here the treatment is surgical whenever the location and clinical findings warrant it and the patient's general condition permits. After giving a brief review of the surgery of atherosclerosis, Professor Rob puts forward the suggestion that surgeons will soon be treating many more stenosed, as opposed to thrombosed, arteries. He makes a particular point of the value of arterial auscultation in the diagnosis of arterial stenosis.

ACROPARÆSTHESIAS AND THE CARPAL-TUNNEL SYNDROME

Pain and tingling in the arms and hands during pregnancy are fairly common symptoms, but relatively little attention has been drawn to them as they often do not arise until the last three months of pregnancy, and they tend to improve after delivery. In a series of 14 pregnant patients reported by Wilkinson (*Lancet*, 1: 453, 1960), seven had compression of the median nerve only and the other seven had signs of median nerve compression combined with signs of compression of one or more cervical nerve roots, suggesting a common pathogenesis. She suggests that trauma (e.g., from household jobs), a rapid or unusually great increase in weight, and hormonal relaxation of the carpal ligament are the main etiological factors.

Compression of the median nerve in the carpal tunnel has also been described in acromegaly and myxœdema, in which conditions the connective tissues swell. There is no doubt also that the radicular symptoms of cervical spondylosis include acroparæsthesias: and, previously, acroparæsthesias were usually ascribed to disorders of the thoracic inlet.

Acroparæsthesia, then, is a symptom which may indicate disturbed function of the sensory nerves supplying the hand at one of three points in their course—the intervertebral foramina, the costoclavicular region, or the carpal tunnel. Before rational treatment can be begun both the site and the nature of the lesion must be determined.

TREATMENT OF SYPHILIS

"The increase in syphilis, beginning nationally in 1956, in Massachusetts in 1954, and continuing to the present, has caused many physicians to renew their acquaintance with this highly versatile disease." The author, N. J. Fiumara, who is a director of the Division of Venereal Diseases of the Massachusetts Department of Public Health, in addition to his duties at the Boston University School of Medicine, describes methods used for dealing with syphilis in its various forms (*Connecticut Med.*, 24: 78, 1960).

The total of 12 million units of penicillin for neurosyphilis and six million units for all other forms is satisfactory. Patients are examined clinically and serologically once a month for a year after treatment. In the second year the interval is three months and, if the Wassermann is fast, annual examination is carried out thereafter.

Contact interview is stressed and other important aspects of treatment and management are outlined. The Jarisch-Herxheimer reaction can be expected to occur in 90% of cases of secondary syphilis after the first injection of penicillin. Reduction of the initial dose will not prevent this and under no circumstances should treatment be withheld or discontinued because of this reaction.

(Continued on advertising page 28)

Canad. M. A. J.
April 23, 1960, vol. 82

Men and Books

MONTREAL NEUROLOGY*

JEAN SAUCIER, M.D., F.R.C.P.[C.], *Montreal*

Some six months ago I delivered a short after-dinner address in which I commented briefly on the evolution of neurology in Montreal. I then emphasized, as one would have expected, the importance of that mecca called the Montreal Neurological Institute and I focused my remarks on the agglutinating and chemotropic influence of the Montreal Neurological Society which created, so to speak, a common appeal to all neurological endeavours around the recently inaugurated dynamic mother-house. I recalled the proselytism of the pioneers and I described the fast pseudopodial invasion of French and English colouring which rapidly extended into the major centres of our province. I attempted an historical presentation of the subject and I had recourse to a convenient, existential division stemming from the Husserlerian category of *time* into the pre-Penfield and the post-Penfield eras. I elaborated a good deal upon the post-Penfield achievements for obvious reasons. However, the need for a new edition of the same subject promoted some historical research and deeper reflection, to such an extent that I discovered that Montreal neurology actually started with Ville Marie. It commenced right away with neurosurgery. It is common knowledge that the Iroquois were very skillful in the art of cutting scalp flaps of various dimensions in record time. Unfortunately, their motivation was more sadistic than scientific. I have been told that some psychoanalytically inclined historians of medicine have not hesitated to imagine a certain *rapprochement* between the savage scalpings of the Indians and the often too complacent carvings of certain neurosurgeons! Such malicious remarks must have come from the glib tongues of mischief-makers. Of course no one ever believed such abstruse connotations.

* * *

Although a great deal remains to be discovered or reassessed in the intricate and often elusive mechanisms of the central nervous system, it has been universally acknowledged that neurologists have already clarified several research hypotheses. Time and teamwork have been the paramount factors in such glorious results. The chief merit of our director was his acute awareness from the very beginning of the need for adequate cooperation and his application of multidirectional approaches to all research endeavours.

It is indeed most appropriate to recall at this solemn moment Dr. Edward Archibald's invitation. Canada's first brain surgeon did not hesitate to use his own prerogative to offer a fresh and enlarging field to newcomers. Dr. Penfield and Dr. Cone answered the call with enthusiasm. This was October 1928. The challenge was an enormous one because neurology was and still is the greatest unexplored field of medicine.

Dr. Penfield once said that the brain is the "dwelling place" of a man's soul, the machine without which the mind does not exist. He went on to add that it is the physical basis of the mind, the "seat of the soul" if one prefers. Taking advantage of his ability as a biologist he elaborated further, surmising that the spirit is present as long as the brain functions, and, fostering a definitely spiritual viewpoint, he suggested that we may believe that the spirit comes from somewhere and goes somewhere. He is too genuinely fascinated by the pursuit of exact knowledge and of freedom to impose his personal beliefs upon his listeners and followers. They may choose from a variety of hypotheses including the mystical approach. Incidentally, George Bernard Shaw, the Irish Marivaux, is reported to have had the government of his thoughts led by what he termed "mystical assumptions".

Thinking in terms of etiology before therapy, which inevitably follows, Wilder Penfield created a body of basic science based upon efficient teamwork.

* * *

The arrival of Dr. Penfield and Dr. Cone in Montreal was hailed with rapture by French-speaking and by English-speaking neurologists as well, by both universities, by the Ministry of Health and by civic authorities. Almost simultaneously, the Rockefeller Foundation supported the nascent initiative by an endowment fund which resulted in the erection of the Montreal Neurological Institute. Numerous other benefactors quickly followed and entered into friendly rivalry as regards generosity. They are too well known to require enumeration. Furthermore, I presume that genuine benefactors do not wish to have their services too often and too loudly proclaimed. Giving implies an unobtrusive gesture.

* * *

Other speakers will recall the avatars and vicissitudes of the M.N.I. during the past 25 years: the episodic nightmares of financial tightening, the war years, the building expenditures, the facing of appalling deficits, the constant reorganization projects and the tremendous development of research. The M.N.I. rose rapidly to universal recognition and is presently hailed as the world's best teaching centre of neurological sciences. Its achievements have been widely publicized in the press of five continents, and the collected papers of its members would represent some 800 or 900 publications in several languages.

* * *

In the dramatic evolution of neurology in Montreal, one must agree that the M.N.I. has been the pivot of the growing tempo of that specialty. Consequently, it is still apropos to envisage the temporal experience in terms of pre-Penfield and post-Penfield periods.

It is no secret that during the first quarter of the twentieth century neurology was more or less the poor relative of medicine. Neurosurgery was a vague research project in the hands of a few daring explorers of "terra incognita cerebralis". Those were the days when progressive, sly and well-informed neurologists sent their neurosurgical patients to Boston and Baltimore. The local pioneers of these lustreless neurological decades were Colin Russel, Fred MacKay and Albert Prévost.

Colin Russel had a pronounced British accent which he likely acquired during his long sojourn at Queen's Square. He also was a talented figure painter and a colonel in the army. He invented a wily gadget to expose malingerers who simulated diplopia or monocular blindness. Fred MacKay, his black-browed and

*Read at the Quarter Century Celebration of the Montreal Neurological Institute, October 6, 1959.

Author's address: 1414 Drummond St., Montreal 25, Quebec.

white-haired brother-in-arms of the Montreal General Hospital, used to test his patients more or less routinely with the faradic brush; whether consciously or not, he was a fervent disciple of Duchenne de Boulogne. Howbeit, he was a witty and sympathetic colleague and an excellent after-dinner speaker. Albert Prévost came back to Montreal after a stay of seven years at the Salpêtrière in the service of Prof. Déjerine. He died in a car accident in 1926. He was a well-trained neurologist. Unfortunately circumstances compelled him to veer early to psychiatry because a mammoth clientele of allegedly nervous patients urged the neurologist to treat their sick "nerves". Very soon his true neurological cases did not exceed 10% of his patents. He then became a self-made neurological psychiatrist and his unabating success prompted him to found the Institute which still bears his illustrious name. He probably was a born psychiatrist because he did not practise his art with reluctance. He was the victim of success. His magnetic personality may well be summarized in two evangelic words: kindness and humility.

I should also mention our dear, durable and enthusiastic neuropsychiatrist Norman Viner who had already started flirting outrageously with the occult sciences, and Emile Legrand, an excellent neuropsychiatrist and in addition a typical *bon vivant*. He was at his best when confronted with the evaluation of neuropsychiatric disabilities.

Then came 1928 with the arrival of Penfield and Cone. Arthur Young was already an associate of Colin Russel, and Norman Petersen was the first registrar of the Institute. Including the abovementioned, the first medical staff of the M.N.I. consisted of Roma Amyot, Donald McEachern, Francis McNaughton, A. G. Morphy and myself.

Then, with the passing of years came Jasper, Hoen, Evans, Erickson, Grant, Kershman, Stern, Prados, Barbeau, Caron, Cipriani, the two Elliotts, Rasmussen, Fisher, McRae, Robb, Bailey, Desrochers, Lloyd-Smith, Swank, Rabinovitch, Graham, Tatlow, Feindel, Heller, Olszewski, the two Bertrands, Tower, Howell, Cosgrove, Roberts and so many others as years added to years, including a long list of fellows and residents of all nationalities, among whom I cannot forget Courtois, Gauthier, Bélanger. I know that I have omitted several among the most brilliant representatives of Montreal neurology, but I never intended to set up a catalogue or a personal index.

* * *

A special *in memoriam* mention should be given at this time to all those who should be here today, 25 years after the opening of the Institute. J. N. Petersen died in 1944, in harness, after having written his annual report in bed in the Residents' suite of the Institute, of a crippling and painful illness. He was the first permanent staff officer to depart. I should also mention the passing of Legrand, Russel, MacKay, McEachern, Barbeau and Kershman, all at the height of their productivity. Most recently, William Cone was struck off the list of pioneers. He left us on schedule, during the night, after having inspected several dressings according to his incorrigible practice. His mode of departure fitted his way and philosophy of life, for such was his mystical *Dasein*. As Francis McNaughton suggested, he set an example that no one can follow. Dr. Cone's death will certainly change the scene of neurology at the M.N.I., at least the night outlook. For a long time we will miss his vivifying enthusiasm, his inventiveness and his contagious charity.

* * *

The annual Hughlings Jackson lectures and other semi-official events have been graced by the most celebrated names in neurology. I shall quote at random Kinnier Wilson, Spielmeyer, Pierre Masson, Sir Francis Walshe, Th. Alajouanine, Percival Bailey and a score of other outstanding exponents of *res neurologica*.

Mentioning all those who published epoch-making contributions to neurology would mean the setting of an alphabetical table of several hundred names. I would rather omit the names of the authors and replace them instead by the themes of the contributions. It would then be easy to identify the original writer.

Epilepsy is certainly the most often and most exhaustively tackled problem. It has been scrutinized in all its facets. Papers on epilepsy alone could have hurled the name of the Institute into the orbit of fame. Investigations on epilepsy caused the cerebral cortex to be revisited with increased inquisitiveness in its gross and histological anatomy, while original vistas have been opened on heretofore obscure physiological mechanisms. The pituitary gland has been submitted to experimental and technical revisions of audacious thinking. Biographies of illustrious neurologists of the past have been drafted and rewritten with the most painstaking insistence. Cerebrovascular syndromes and cerebral circulation became the fruitful field of valuable and original discoveries and of rejuvenated conceptions. Trauma, actual and experimental, captivated the attention of many; neurologists and neurosurgeons have probed deeply into the matter of head and back injuries. Their routine management is the result of keen observation and constantly improved diagnostic and therapeutic techniques. Cranial nerves received close and elaborate study; each one of them, at least, has been reviewed hypercritically as regards function, anastomoses, relations with adjacent structures, regeneration and degeneration. Studies on cerebrospinal fluid circulation have been proceeded with along its normal channels and those invented by artificial therapeutic shunts. Articles on electroencephalography are innumerable. Many are presently acclaimed as unmistakable milestones or "le dernier mot" in most neurophysiological laboratories.

The problem of pain has been approached both etiologically and therapeutically at all levels of the cerebrospinal axis.

Among research topics, tumours of the nervous system are probably responsible for the greatest number of scientific publications, including clinical behaviour, diagnostic procedures, histological identification and statistical studies.

From the very beginning, chemistry and pharmacology have played a part of importance, and routinely neurochemists have become indispensable ministers in the realm of neurology. The enigma of multiple sclerosis has had and still has its squad of close observers. Neurological aspects of war neuroses have been investigated in friendly co-operation with psychiatrists.

Radiology under its two authoritative exponents deserves mention as a first-rate adjunct in the achievements of the Institute, perhaps because of the peremptory and spectacular character of its decisions. Medical photography and cinematography have recorded imperishable documents of rare clinical kinetic behaviour,

Canad. M. A. J.
April 23, 1960, vol. 82

pathological material that defied accurate description, and surgical skill.

As might be expected, herniations of brain at all levels and protruded intervertebral discs have been the theme of many papers. Basal nuclei have been studied exhaustively with their afferent and efferent fibres; surgical and pharmacological techniques for ensuring their proper functioning have been described in numerous publications. Infections of the nervous system and meninges have held the careful attention of both neurologists and neurosurgeons. The same interest has been invested in vitamin deficiencies and metabolic disorders. Experimental work on motion sickness has been too frequently publicized to labour the topic further. Even lobotomy has had a definite trial but for reasons of uncertain motivation it has not been carried out on a large scale. Speech, memory, aphasia, agnosia and consciousness have been the subjects of important and decisive clinical and pathological documents to be lodged in the overflowing record of unsettled knowledge.

Hereditary and familial diseases, neuromuscular disorders, and endocrinological inadequacies related to neurology have received the same inquisitive attention and have become the subject of many a stimulating contribution.

* * *

You will agree by this time that naming all those who published neurological papers in the course of the past 25 years would have been too awkward a task to undertake. Gazing at the jubilee mural at the Institute should help us to identify many of them easily.

* * *

The steadily increasing importance of the M.N.I. has made it the firing ramp whence satellites are launched into the world where they enter an orbit of their own. Even at the Montreal level the same phenomenon is on record. Far from causing a waste of energy, such a periodic dispersion contributed to increase the prestige of the Institute and of Montreal, both in Canada and abroad.

Simultaneously the Montreal Neurological Society was founded, and it appears that since its inception it has exerted a decisive catalytic influence, initiating an unavoidable decentralization, provoking free discussion and stimulating the appeal for publication. Friendly competition has promoted full scope of expression in a climate of clinical harmony. The Society has created unexpected opportunities to pool the resources of all neurological sciences. It has kept its members up to date on the relationships of all basic sciences with neurology. It is worth underlining that meetings are conducted in French and English, which does not seem to embarrass listeners to either language except for an occasional multilateral earache or a nauseating hiccup of short duration. The Society has evolved into a very sophisticated group. It is the spiritual link between diverse neurological conceptions while the M.N.I. remains the solemn lighthouse in an erstwhile foggy night which becomes more and more *eine verklärte Nacht.*

* * *

Notwithstanding such glory and grandeur, the case of neurology remains a very complex one. Why are there so few full-time neurologists as compared with other specialists—psychiatrists for instance, to take an example at random? I have tried answering this question elsewhere in 1953 but my remarks have found no echo and have given rise to no exchange of comments.

It is doubtful that neurology, unassisted and isolated, would be a viable concept. So many allied disciplines have already grafted on neurology that it is most likely that we might completely lose sight of the fundamentals unless all subdisciplines were incorporated in a harmonious whole. Dispersion was the imminent danger but the M.N.I. and later the Montreal Neurological Society have achieved that salutary polyvalent oneness so desperately needed. In other words, neurology cannot exist alone. It should be buttressed by the arsenal of all neurological sciences. Neuropsychiatry is a compromise that has its merits but it usually means after a while a decision in favour of one or the other. Neuropsychiatric thinking, however, should never desert the mind of a true neurologist or a genuine psychiatrist.

At all events, I cannot help being a little pessimistic over the future of our specialty unless we watch carefully the advent of untimely excrescences. In our age of overspecialization, neuroelectronics, neuroballistics, neuroatomistics and many other new hybrid hyphenated specialties of our enlightened century may become the caricature and disfigured distortion of our noble art, the art of Gowers and Pierre Marie. Since we cannot stop the inexorable march of time, we must beware of premature thinking and excessive technology. We must remember that apparent progress is often coupled with regression or regression-provoking consequences. I cannot help recalling the joy and beauty of two little incidents which occurred a long time ago: in 1929, Wilder Penfield operated on a patient of mine for a meningeal fibroblastoma at the level of Th.6 without a myelogram. We simply repeated our sensory examination more carefully because extreme precision was then paramount. Not long after, he operated on an epileptic merchant from Joliette for a left temporal glioblastoma without an EEG and without a pneumogram. These were the days when the art of examining neurological patients carried a sacred significance. Nowadays, mechanical aids and improved techniques can do the work much more quickly and perhaps more accurately but joy and beauty have been replaced by imperturbable and impersonal pseudo-contentment. Systematized routine questioning is the modern way of talking to patients. We have saved time, but have we accepted the responsibility of using the precious salvaged moments with discrimination? Should machines henceforth unequivocally replace first-hand clinical information, we shall be forced to acquiesce with nostalgic reluctance.

This short article is not meant to become a technical survey. It is hardly more than a rapid glance at 25 neurological years in Montreal. First and foremost is the apotheosis of an Institute and that of its leader. It is obvious that this incomplete recital of historical events has been permeated with the constant presence of Wilder Penfield. He has attained his purpose through concentration, inspiration, labour and love. I should like to add a concluding remark: the author of *No Other Gods* is also a poet. He has taken from poetry through recollection of emotions in tranquil meditation the extra stimuli that have gradually been transformed into majestic achievements. Paraphrasing President de Gaulle's glorious slogan, there is no M.N.I. without grandeur. Wilder Penfield, in the name of your colleagues, friends and associates, I bestow upon you, with our affection, admiration and gratitude, the symbolic order of neurological merit.

MEDICAL SOCIETIES

MONTREAL PHYSIOLOGICAL SOCIETY

The second regular Scientific Session for the year was held at Queen Mary Veterans Hospital on Monday, March 7. The Special Lecture by Dr. Peter B. Dews, associate professor of pharmacology, Harvard Medical School, was given from 5 to 6 p.m. in the main auditorium of the hospital. He spoke on "Effects of drugs on some time-dependent aspects of conditioned behaviour". Special efforts have been directed towards qualitative assessment of affects of drugs on behaviour. A pioneer worker on the effects of drugs on the C.N.S., Dr. Dews reported on recent studies using pigeons as test animals. A buffet supper provided through the courtesy of the Queen Mary Veterans Hospital, Department of Veterans Affairs, was served in the Board Room.

Eighty-three were present for the buffet supper and at 7 p.m. a brief business meeting was held when seven new members were accepted into the Society and the date of the final meeting for the year set. Then followed the scientific session, held in the Auditorium, with eight presentations.

Drs. B. G. Benfey, G. Ledoux and K. I. Melville of the department of pharmacology, McGill University, reported on a hypertensive phase of phenoxybenzamine action.* The injection of the antisympathomimetic drug phenoxybenzamine (Dibenzyline) in dogs under pentobarbital anæsthesia after treatment with ganglion-blocking drugs caused a marked rise of blood pressure instead of the usual fall. In the spinal dog phenoxybenzamine showed a hypotensive effect. The results suggest that ganglion-blocking drugs sensitize vascular excitatory adrenergic receptors to the action of adrenaline and noradrenaline, which occur in increased amounts in plasma and urine after phenoxybenzamine and the antisympathomimetic effect of phenoxybenzamine is overcome.

Dr. V. W. Adamkiewicz of the department of physiology, University of Montreal, showed that insulin-Zn (40 u./kg. s.c.) in the rat prolongs two- to four-fold the cardiac action (rate) of the glycoside k-strophanthin (10-20 mg./kg., s.c. or i.p.). Insulin also increases by 20% the mortality of rats overdosed with k-strophanthin (30 mg./kg. i.p.), but simultaneously retards six-fold the time of death. On the other hand, insulin appears not to affect the cardiac action of the aglucone strophantidin.

Drs. L. Pinsky and F. Clarke Fraser of the department of genetics, McGill University, presented evidence that congenital malformations will occur following only a two-hour inactivation of nicotinamide by its analogue 6-aminonicotinamide. Pregnant mice were treated with 6-aminonicotinamide (20 mg./kg.) and nicotinamide (7 mg./kg.). When given simultaneously, no malformations occurred in the offspring. With the nicotinamide given two hours after the 6-NH_2-nicotinamide, malformations did occur, including hind-limb defects and cleft lips by treatment on day 9, a high frequency of resorptions on day 10, and cleft palates on day 11 (the day a vaginal plug was observed was counted as day 0). This raised the question whether a two-hour inhibition of nicotinamide activity was teratogenic, or if, perhaps, the nicotinamide injection at two hours did not completely counteract the effects of the analogue. If the latter were the case, then a double dose (14 mg./kg.) of nicotinamide given at two hours would be expected to give a lower frequency of defects than the single dose. On days 10 and 11 the double dose of nicotinamide did not lower the frequency of defects, but on day 9, it did. These results are interesting as a way of getting fairly precisely timed embryonic exposures to a biochemical deficiency, and also because they suggest that there are variations in the metabolic requirements of the embryo from stage to stage.

Dr. A. Wechsler, department of physiology, McGill University, studied the secretion of submaxillary salivary electrolytes in the neo-natal and young dog.* At birth the secretion is nearly isotonic, the main constituents being sodium and chloride. The bicarbonate concentration is exceedingly low. With increasing postnatal age, the tonicity of the secretion falls, as do the sodium concentration and the ratio of chloride to bicarbonate. These results emphasize that tubular and duct-like structures in the young gland must be responsible for most of the secretion at that stage.

Dr. R. A. Millar of the Montreal Neurological Institute reported on studies to assess the effect of Tris (hydroximethyl) amino-methane (T.H.A.M.) on circulating catecholamines and acid-base balance during prolonged apnœa in dogs. As a result of T.H.A.M. administration, arterial oxygen saturation was maintained during apnœa, and plasma adrenaline and noradrenaline remained at near-normal levels. When given in the presence of an already existing severe respiratory acidosis, T.H.A.M. infusions were effective in producing a rapid fall in pCO_2 and plasma catecholamine levels, with a rise in arterial pH, "standard" bicarbonate, and arterial oxygen saturation. These findings are in broad agreement with the preliminary report of Nahas (1959).

Drs. C. R. Branch, M. Morris, and R. A. Millar, departments of neurosurgery and anæsthesia, Montreal Neurological Institute, reported on preliminary attempts at extracorporeal cerebral circulation in dogs. It is considered that separation of the cerebral from the systemic circulation would broaden the scope of present-day neurosurgical procedures. Current studies in dogs are directed towards this end, and involve bilateral cannulation of the carotid and jugular vessels and the use of a DeBakey pump, with a bubble oxygenator primed with blood from two donor dogs. A low arterial inflow rate (5 ml./kg./min. or less) and a balanced venous outflow have been found essential for survival. The major problems so far encountered, of which most have been those presented by the pulsatile flows and pressures produced by pumps designed for total body perfusion, are now being circumvented by using a gravity pressure head for carotid perfusion. Survival without sequelæ has followed brain perfusion for periods of 30-60 minutes with subsequent suturing of the carotid and jugular vessels.

Dr. R. B. Goldbloom, Montreal Children's Hospital, investigated tocopherol deficiency in infancy and childhood. It is now possible to delineate certain biochemical and histological changes which together

*This work was supported by a grant from the National Research Council.

*Supported by a grant from the National Research Council.

Canad. M. A. J.
April 23, 1960, vol. 82

constitute the known features of tocopherol deficiency in man. Low levels of serum or plasma tocopherol, increased erythrocyte hæmolysis in hydrogen peroxide, creatinuria and increased plasma creatine in steatorrhœic diseases, and the ceroid pigmentation of smooth muscle and in hepatic portal macrophages are the chief proved elements of this condition. Investigations of the incidence and manifestations of tocopherol deficiency in man were presented, and the nutritional role of tocopherol in health and disease was discussed. Their results suggest that tocopherol supplementation in infants, especially in immature infants, needs further study. This is in progress.

Drs. R. M. Buckle, D. Rubenstein, E. G. McGarry and J. C. Beck, McGill University Clinic, Royal Victoria Hospital, reported on the influence of glucose and insulin on the liberation of non-esterified fatty acids from rat adipose tissue. Their work confirmed the finding that glucose and insulin markedly inhibited the release of NEFA from the fat pad (Gordon and Cherkes, 1958). The ability of glucose to inhibit the release of NEFA persisted under anaerobic conditions. Possible mechanisms of the action of glucose were discussed. A. H. NEUFELD

THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

The President of The Royal College of Physicians and Surgeons of Canada, Dr. Donald A. Thompson, has announced the initiation of an important national development in the interchange of medical knowledge between Canadian medical schools and other world centres of medical education and research. The R. Samuel McLaughlin Foundation has granted an amount of $6000 to provide a Visiting Professorship in Canadian medical schools. It is understood that on annual application the Foundation will view favourably the continuation of this grant.

The Professorship will be known as the McLaughlin Foundation Edward Gallie Visiting Professorship in The Royal College of Physicians and Surgeons of Canada. It will commemorate the service to his fellow men and the outstanding contributions to surgical science of a great Canadian surgeon, Dr. William Edward Gallie of Toronto, who died in September 1959. Dr. Gallie was Professor of Surgery in the Faculty of Medicine in the University of Toronto until he retired in 1947. He retired as Dean of the Faculty in 1946.

It is planned to select a distinguished medical scholar from some centre, who will spend at least a month in visiting one or more Canadian medical schools, lecturing, teaching, and exchanging ideas with the staff, research workers, and students in the Canadian centres. It is understood that the visitor may be chosen from any country in the world, and may represent any of the clinical fields—medicine, surgery, obstetrics, or any of their special branches.

The College has established a Joint Committee with representatives from the Association of Canadian Medical Colleges, and this committee will undertake the selection of the first Visiting Professor, as well as the Canadian arrangements for the selection of the school or schools to be visited.

The R. Samuel McLaughlin Foundation was established in 1951. Since that time it has spent approximately one and a half million dollars in support of various educational efforts in Canada. One very important feature of the work of the Foundation is the provision for Travelling Fellowships in the Faculties of Medicine of Canadian universities. These Fellowships enable young medical graduates who have been selected as teachers and investigators in Canadian medical schools and their associated hospitals to travel to other centres in any part of the world. Thus at a critical period in their professional careers, they have the opportunity to gain special knowledge and experience in their particular field of endeavour.

LETTERS TO THE EDITOR

RHEUMATOID ARTHRITIS AND AGAMMAGLOBULINÆMIA

To the Editor:

I wish to make reference to the report entitled "Rheumatoid arthritis and agammaglobulinæmia," which appeared in a recent issue of the Journal (82: 81, 1960). The combination of disabilities affecting the patient under consideration is indeed unique and as such merits being recorded in the medical literature.

The statement relative to the rarity of acute pyogenic arthritis due to the *Hæmophilus influenzæ* organism, with no case having been reported in the past 15 years, is one which should be qualified.

Dyer and his co-workers reported[1] a case of *Hæmophilus influenzæ* arthritis about 1½ years ago. In their report they review the literature on this condition, and cite 31 cases which had been documented over the period 1899 to 1957. This report nothwithstanding, septic arthritis due to *Hæmophilus influenzæ* is still rather unusual.

GEORGE X. TRIMBLE, M.D.,
Director of Medical Education
Seaside Memorial Hospital of Long Beach,
Long Beach, California,
February 29, 1960.

REFERENCE

1. DYER, R. F., ROMANSKY, M. J. AND HOLMES, J. R.: *A.M.A. Arch. Int. Med.*, 102: 580, 1958.

MOUTH-TO-MOUTH RESUSCITATION

To the Editor:

The rescue of a life during that short period between the failure of respiration and the onset of irreversible anoxic damage is a great achievement. Since the dawn of modern medicine much thought and ingenuity by great men in our profession have been devoted to this problem; a recent publication by Dobkin in this Journal (81: 458, 1959) gives an excellent account of the history of artificial respiration. At present, we are experiencing the renaissance of a method of biblical times which has been advocated at intervals during the past two centuries without receiving much support—mouth-to-mouth breathing or expired air inflation.

A major contributing factor to this revival undoubtedly has been the demonstration of the safety and efficiency of intermittent positive pressure breathing which is practised now almost universally by anæsthetists. The suspected dangers of positive pressure breathing, rupture of alveoli and interference with the return of blood to the heart, have been found to be of minor practical importance compared with the immense benefits of this method.

This new era in resuscitation began officially with a symposium on expired air inflation published by the *Journal of the American Medical Association* (167: 317, 1958), after earlier work by Elam, Brown and Safar. Other publications, comparing the efficiency of expired air inflation with the various manual methods of artificial respiration, have appeared since and have all confirmed the superiority of this "old" method in regard to the maintenance of an adequate ventilation and oxygenation. Another recent report consists of a symposium by Killian, Ulmer and co-workers in the *Deutsche Medizinische Wochenschrift* (85: 53, 1960), which is the basis for the present comment.

Manual artificial respiration requires a considerable physical effort, while the exchange of alveolar air is more often than not inadequate to maintain normal arterial oxygen saturation and arterial CO_2 level. X-ray studies (Killian) show that with the method of Silvester good chest wall movements and fairly good diaphragmatic movements can be demonstrated in subjects with a normal muscle tone; in fully paralyzed subjects, however, the chest wall expands poorly during inspiration and the diaphragm remains immobile and may even follow the negative intrathoracic pressure in the form of a paradoxical movement. The compression of the chest wall during the expiratory phase of this method does little to reduce the thoracic volume; particularly in elderly patients with a rigid thorax this method is very inefficient. Killian concludes that this technique, while probably effective in lightly depressed cases, is inefficient in subjects paralyzed by profound anoxic depression. In the latter, an inflation of air with a low pressure readily expands the chest.

The airway is of decisive importance, and Ulmer found it practically impossible to ventilate a paralyzed subject (using the methods of Thomson, Sylvester and Nielsen) even in the prone position unless a second rescuer attended to the airway. With endotracheal intubation the methods of Sylvester and H. Nielsen proved adequate.

Mouth-to-mouth resuscitation has the advantage of an easier inflation of the lungs and leaves the hands of the rescuer free to support the airway. Consequently an adequate alveolar ventilation of the lungs is achieved in a very high percentage of cases, and the oxygen content of expired air is sufficient to maintain a normal oxygen saturation. The danger that an eager rescuer might suffer from a hyperventilation syndrome is probably minimal, but should be realized.

Much more important are æsthetic considerations, which have stimulated the invention of several types of tubes, interposed between the patient and the rescuer. The idea of a pharyngeal airway, as recommended by North American authors (Safar, *J. A. M. A.*, 167: 335, 1958); Brook and Brook, *Canad. M. A. J.*, 82: 245, 1960), is rejected because of the difficulty in inserting such an airway and the possibility of initiating vomiting by stimulating pharyngeal reflexes.

Finally, the practical management of expired air inflation must be considered; a clear airway is obtained best by maximal extension of the head and by pulling the jaw upwards. It is felt that mouth-to-nose breathing is probably easier to perform, provided the nasal passage is clear; it also gives a lower incidence of air inflation into the stomach.

All studies using curarized subjects have unanimously shown the superiority of expired air inflation when compared with the various manual methods of artificial respiration; even laymen with almost no instruction have been able to maintain a normal oxygenation. It is probably hypercritical to ask whether the resemblance between a person paralyzed with curare and a person in respiratory arrest due to drowning, electrocution, suffocation or head injury is close enough to allow a comparison. Also, in practice the æsthetic factor could weigh heavily; it requires a good deal of courage to perform unaided mouth-to-mouth resuscitation in an unconscious person who has just vomited, and a fainting spell of the rescuer does not further the rescue. Yet, the various aids to expired air inflation are usually not available and precious time may be lost in procuring or inserting such devices.

Theoretically, expired air inflation has many advantages over the manual methods; it is simple, it can be started readily and without undue effort, and it has the best chance of producing adequate pulmonary ventilation. It should be advocated by all means, and it should be taught without any devices or aids in its pure form. But its practical application must be thoroughly tested before the methods of manual artificial respiration are completely discarded; after all, these have saved many lives in the past.

459 Coombs Ave., W. E. SPOEREL, M.D.
London, Ont.,
March 15, 1960.

THE PLACENTA IN SKIN GRAFTING

To the Editor:

An article in the Civil Defence issue of the *Canadian Medical Association Journal* (March 1, 1958) prompts this letter. The author states that homografts may be taken from living donors or cadavers in cases of severe extensive burns where areas for autografts are not available.

I have in one case used the amniotic layer of the placenta as a source of epithelium in a severely burnt Metis patient. Unfortunately the large area on her abdomen which was grafted became infected and I could not be sure of a take. However, the site did not require subsequent autografts.

It is apparent in our atomic age that any future conflict would result in a large number of burned cases. Has any previous work been done on using the amniotic layer in burn cases? The chorionic and amniotic layers separate readily in saline solution and its availability and fresh daily supply are evident. I would appreciate hearing from anyone who knows whether or not attempts have been made and of their outcome.

J. STORCER, M.D.

Grande Prairie, Alberta,
March 17, 1960.

Canad. M. A. J.
April 23, 1960, vol. 82

OBITUARIES

DR. JAMES A. CAMPBELL, 82, died in the Barclay Nursing Home, Hamilton, on February 20 after a long illness. Born in Keene, Ont., he graduated in medicine from the University of Toronto in 1905. He practised in New York City for many years.

DR. ARTHUR S. CHESLEY of Saint John, N.B., died suddenly on March 12 at Sarasota, Florida, where he was visiting friends. For some years he had spent part of each winter in Florida since his retirement in 1955. Dr. Chesley was born in Saint John in 1897. After schooling in Saint John, he attended Dalhousie and McGill Universities, graduating in medicine from McGill in 1923. He served his internship at the Saint John General Hospital and did postgraduate studies in urology in New York Post-Graduate Hospital. In 1945 he was appointed the first chief of service in the Urology Division of Surgery at the Saint John General Hospital. He was a skilful fisherman and hunter and had an unusual gift of friendship.

Dr. Chesley is survived by his widow and two sons, Dr. Arthur E. Chesley of Saint John and John C. Chesley of Montreal. A.S.K.

DR. HAMNETT A. DIXON, 66, died in Sunnybrook Hospital, Toronto, on March 7. Born in Ottawa, he studied medicine at the University of Toronto and graduated in 1916. Later he went to London, England, for postgraduate studies. During World War I, Dr. Dixon served overseas as medical officer with the No. 4 Canadian General Hospital, and later he became a major in the R.C.A.M.C. reserve. Dr. Dixon was an associate professor of medicine, emeritus, at the University of Toronto and consultant dermatologist to the Toronto General Hospital and the Hospital for Sick Children. He was a member of the Academy of Medicine of Toronto and of the Canadian and American Dermatological Associations.

Dr. Dixon is survived by his widow and a daughter.

DR. HAMNETT A. DIXON

AN APPRECIATION

Dr. Hamnett A. Dixon was the last of the founding members of what has become the Canadian Dermatological Association. He was one of a small group who, in 1926, conceived the idea of a national dermatological association. He served this Society well throughout the years, and seldom missed a meeting. He always believed that this Society should be closely allied to the British Dermatological Association and spent much time fostering this alliance.

He served in the various offices of the Society and was appointed Chairman of the Section of Dermatologists for the joint C.M.A.-B.M.A. meeting in Edinburgh in 1959.

For many years "Ham" Dixon has been one of our elder statesmen. One looked forward to his friendly greeting and cordial smile at the meetings. He enjoyed entertaining his colleagues and was always a charming host. To many of us he was a teacher, a colleague and a friend. He will be sorely missed. R. ROY FORSEY

DR. BEVERLEY C. LEECH died on March 10, 1960, aged 61. Dr. Leech, who had been practising medicine in Nanaimo for the past three years, was a man of distinction, both in his profession and as a soldier. As a doctor he early specialized in anæsthesia, and was one of the first four men obtaining specialist qualifications in Canada. He practised in Regina for 26 years. He was a Fellow of the Faculty of Anæsthesia, Royal College of Surgeons, England, and of the International College of Anæsthetists; he was President of the Canadian Anæsthetists' Society in its early years, and obtained many other distinctions in this specialty.

At the age of 18, he was severely wounded while serving with the 28th Battalion in France in the First World War. He graduated in medicine at McGill University in 1925, and in World War II obtained command of the 10th Field Ambulance in England. He later served in Italy, and at the end of the war was A.D.M.S. of the 2nd Canadian Division in France. He won many military honours, including the *Légion d'Honneur* (*Chevalier*). He was honorary aide-de-camp to the Governor-General of Canada from 1952 to 1957.

In Nanaimo he rapidly became an outstanding practitioner and was immensely popular, both with his patients and with his colleagues in medicine. Those who knew him had for him a deep sense of admiration and affection. He leaves his widow and a son.

DR. JOHN M. LEES, 44, died in an Edmonton hospital on February 26. Born in Amisk, Alta., he studied medicine at the University of Alberta, graduating in 1938. In the Second World War Dr. Lees served with the R.C.A.F. and attained the rank of Wing Commander. He was discharged from active service in 1945, but remained with the R.C.A.F. reserve until 1949. Since 1939 Dr. Lees has been associated as a surgeon with the Baker Clinic in Edmonton. He was chief medical officer for the Northern Alberta Railway and C.N.R. house physician at the Macdonald. For four years he was president of the board of directors of Medical Services (Alberta) Inc. Dr. Lees was a member of the Canadian Society of Clinical Surgeons, Western division, and was a lecturer in clinical surgery at the University of Alberta.

His widow and four children survive him.

DR. WILLIAM ALBERT SCOTT, 74, professor emeritus of the University of Toronto, died February 19 at Toronto General Hospital.

Born in Petrolia, Ont., in 1885, Dr. Scott was a gold medal graduate of the University of Toronto, Faculty of Medicine, in 1913. He was an assistant in obstetrics and gynæcology at the University of Toronto and chief of service at the Toronto General Hospital. He was a professor at the university for 16 years.

Dr. Scott was a member of the American Gynecologists Society, a Fellow of the Royal College of Surgeons and past president and Fellow of the Royal College of Obstetricians and Gynæcologists, Canada.

He was the author of a medical textbook and many scientific articles. He served in the First World War with No. 4 Canadian General Hospital Unit.

Surviving Dr. Scott are his widow, two daughters and a son.

PROVINCIAL NEWS

SASKATCHEWAN

The Saskatchewan College of Physicians and Surgeons has adopted a statement of policy which specifically lays down the responsibilities and rights of individual citizens and medical practitioners in all matters governing medical care.

The statement, which was released over the name of Dr. A. J. M. Davies, the President of the Council of the College, was made public because, as he said, "Our patients, friends in industry, agriculture and labour, and members of various political parties have been asking us what we think about this or that health program being advocated or in practice in many parts of the world." As a profession, he stated, "if we are not interested in politics we are not waging a political campaign and we refuse to be engulfed in the battle for political votes. Our fight is to safeguard the health of our patients as individuals and the people of Saskatchewan as a whole. We believe we are fulfilling this trust and we will continue to make improvements as medical science dictates."

Several Moose Jaw doctors spoke at a dinner meeting organized by a citizens' committee which will be assisting in a fund-raising campaign for the $1,250,000 addition to the Providence Hospital in that city. Their professional advice and opinions come at a time when the local voters are considering the plebiscite shortly to be presented by the city asking for authority to make a $182,500 grant to help defray construction costs. The doctors of Moose Jaw stressed the immediate need for the services which will be offered in the proposed addition to the Providence Hospital. This would provide a 20-bed children's unit, a complete new obstetrical floor, operating room, recovery room, food-preparation area and intensive-care unit. Improvements would also be made in the emergency department, medical record room, central supply, and training facilities for student nurses and technicians.

The new construction program would also permit 30 of the present adult beds in congested wards and solariums to be relocated, existing solariums being converted into patients' recreation and visitors' waiting rooms.

A bill has been introduced in the Saskatchewan Legislature to incorporate a "Saskatchewan Society of Public Denturists". This bill is the third relating to the control of the manufacture and fitting of false teeth to be introduced into the House at this session. A bill sponsored by the College of Dental Surgeons of Saskatchewan and one introduced on behalf of dental technicians have already been given two readings.

At present in Saskatchewan denturists may deal directly with the public, provided the customer first obtains a certificate of oral health from a registered dentist or a registered physician. The Dental College wishes to revise the law and prohibit the manufacture or fitting of false teeth except on prescription from a dentist. This could make it appear as if the denturists' main effort would be directed against the dentist bill rather than towards a motion of their own. The terms of the bill make it clear that the Legislature cannot approve both bills as presented by the College of Dental Surgeons or by the denturists.

The technicians' bill also opposes denturists, by requiring all persons making false teeth to be registered under their Act.

At present both technicians and denturists manufacture and repair false teeth, the former doing so on prescription and the latter dealing directly with the public provided the certificate of oral health is available.

Approximately 180,000 patients were admitted to Saskatchewan hospitals in the fiscal year ending March 31, 1959 (about one patient out of every five people in Saskatchewan). This was an increase of more than 2% compared to the previous year.

The present rate of hospital admission per 1000 beneficiaries rose rapidly from 161 in 1950 to 211 per 1000 in 1957. In 1958, the rate dropped to 206 per 1000 beneficiaries. In 1947 the total expenditure of the plan amounted to $9.63 per capita, and in 1958 it increased to $32.14 per capita. Average stay per patient has gradually declined from a high of 11.1 days in 1951 to 10 days in 1958. The present ratio of beds is 7.6 per 1000 population.

In recent faculty changes announced by the University of Saskatchewan effective July 1, 1960, Dr. Melvin G. Kunkel has been named as assistant clinical professor of surgery, Dr. C. W. Baugh as assistant professor of medicine, and Dr. M. J. Smart as assistant professor of diagnostic radiology.

Premier Douglas stated in the Legislature that he believes that province-wide medical-care plans should follow the principle of the hospitalization plan. "Nobody," he said, "here suggests adopting the British Plan. It would not be suitable for Saskatchewan."

According to the 1959 Annual Report of the Saskatchewan Hospital Services Plan, the biggest increase in the number of persons covered in 1959 occurred in the age groups requiring the most hospital services. During the 13-year period since the Plan's introduction the total covered population has increased by 13.8% but beneficiaries 65 years of age and over have increased by 53%. Beneficiaries 70 years of age and over have increased by more than 78%. During the same period children in the age group 1-4 years increased by 41%. Those in the 5-14 years increased by 30%, and covered population in the 15-24 and 25-44 age groups rose 11.4 and 5.2% respectively.

The report also pointed out that the volume of care paid for by the plan in 1959 increased 5.1% over the 1958 experience although the total covered population increased only 2.7%. This difference is accounted for partly by the higher than average increase of population in the older age groups and by the participation of Indians and War Veterans' Allowance recipients.

What may be a first in Saskatchewan's legal history was made during February when Mr. Justice C. S. Davis quashed the verdict of a coroner's jury brought down last November during an inquiry into the death of an elderly Yorktown woman in an accident.

A writ of *certiorari* was granted on the grounds that one of the jurymen had viewed the car that was in-

Canad. M. A. J.
April 23, 1960, vol. 82

volved in the case and the location where it was found after he had been sworn in as a juryman. Mr. Justice Davis wrote that this may or may not have influenced the juryman in the conclusions he arrived at as a juryman. "It would," he said, "be a dangerous precedent to have this verdict stand."

Speaking recently in the Legislature, the Minister of Health, the Honourable J. Walter Erb, assured his listeners that the provincial government would not attempt to regiment doctors, or interfere with their relations with their patients, nor had the government a predetermined plan which it would enforce on the public and the medical profession.

Mr. Erb stated that the province-wide plan proposed by the government would be based on the five principles already laid down—prepayment with individual contributions, high quality of service, universal coverage, administration by a body responsible to the Legislature, and acceptability to the public and the profession. The Advisory Planning Committee would have broad, all-encompassing terms of reference so that it could examine the needs and recommend a program which could be effective, efficient in the best interests of all. "We are unwilling to accept the idea that present voluntary plans are the final answer to the needs of an integrated health service but we do recognize that these plans may have something to offer, and we expect the Advisory Committee to study them and see what use can be made of their techniques, skills and procedures in a program which must be much broader in concept, in scope and in coverage."

The Medical Society of the University of Saskatchewan has passed a resolution opposing the principles of state-controlled medicine. Calling themselves the future doctors of this province, the students passed the resolution at a recent meeting held in Saskatoon, saying, "It is believed that fear of increasing government control is acting as a deterrent to the person of independent character from applying to a medical college", and the result has been an apparent drop in the number of applicants to medical colleges in the past few years. "To these people the possibility of life under bureaucratic control is unattractive" adds the statement.

The Medical Society stated that it was in favour of "privately sponsored prepaid medical insurance schemes, because they reserve the rightful independence of liberty of both the patient and physician. Government-controlled medical practice, by virtue of an employee-employer relationship, makes a doctor's allegiance primarily to the state, not the patient where it properly belongs."

The statement said that the quality of medical care will decline as a result of over-utilization and administrative interference with the professional judgment of the physician resulting in an impersonal assembly-line pattern of medicine.

At the 51st Annual Banquet of the Saskatchewan Optometric Association held in Regina, it was advocated that optometry be considered in an overall prepaid medical-care health plan. It was also suggested that a representative of an optometric body should be included in any planning of the health scheme.

G. W. PEACOCK

ABSTRACTS *from current literature*

MEDICINE

Cycloserine and High-Dosage Isoniazid in Chronic "Treatment Failure" Pulmonary Tuberculosis.

E. WOLINSKY AND V. N. KAPUR: *Am. Rev. Respiratory Dis.*, 80: 269, 1959.

Thirty-five patients with chronic, active, "treatment-failure" pulmonary tuberculosis were divided into three groups and treated for nine to 13 months with either cycloserine alone, cycloserine plus ordinary dosage of isoniazid, or cycloserine plus high dosage of isoniazid. The dosage of cycloserine was 250 mg. twice daily. General improvement was noted in three patients and the progression of disease was halted, at least temporarily, in five others. While still receiving treatment two of the former relapsed and, in addition, nine patients became worse or died. Cultivable tubercle bacilli from the sputum were eliminated in only one patient, but even in this case the sputum became positive again a few months later.

Better results were observed with the multiple-drug regimens than with cycloserine alone, but the larger isoniazid dosage seemed to offer no advantage over the lower isoniazid dosage. Significant toxicity was observed only in the cycloserine—high-dosage—isoniazid group.

Serial cultures from 38% of the patients showed an increase in resistance to cycloserine. It was not possible to demonstrate a clear-cut relationship between *in vitro* resistance and progression of disease. S. J. SHANE

Left Ventricular Hypertrophy Syndrome in Infancy.

S. BLUMENTHAL AND S. O. SAPIN: *Dis. Chest*, 36: 179, 1959.

In infants there is a cardiac syndrome consisting of left ventricular enlargement, without significant murmurs or central cyanosis, and with a tendency to the development of heart failure. Under these circumstances the electrocardiogram may be normal or may reveal evidence of myocardial anoxia or of left ventricular hypertrophy. The authors call this complex the left ventricular hypertrophy syndrome.

This syndrome does not include more commonly occurring cardiac anomalies which produce left ventricular hypertrophy associated with significant murmurs. It does include (1) primary endocardial fibroelastosis; (2) predominantly myocardial disorders, such as (a) idiopathic or aseptic myocarditis, (b) glycogen storage disease of the heart, (c) tumours of the heart, and (d) nutritional deficiency states causing myocardial dysfunction; and (3) disorders resulting predominantly in abnormalities of coronary blood flow, such as (a) anomalous origin of the left coronary artery and (b) coronary occlusive disease.

The demonstration of left ventricular hypertrophy in infancy by physical examination, x-ray film and electrocardiography is discussed, and the usefulness of vectorcardiography is emphasized in delineating pathological right ventricular hypertrophy and thereby excluding the left ventricular hypertrophy syndrome.

The prognosis for survival beyond infancy is grave in these patients and the differentiation from congenital valvular disease difficult. S. J. SHANE

Circulatory Changes in Acute Glomerulonephritis.

V. DEFAZIO *et al.*: *Circulation*, 20: 190, 1959.

Cardiac catheterization was performed in seven patients with the typical clinical and laboratory findings of acute glomerulonephritis in the oliguric phase. All the patients were hypertensive and all but one were œdematous; three had cardiac enlargement, gallop rhythm, and signs of pulmonary congestion. The arm-to-tongue circulation time was measured in six of the patients and was normal.

The chief hæmodynamic findings observed in all patients were as follows: high cardiac output and stroke volume, normal to low arteriovenous oxygen difference, elevated left ventricular filling pressure, normal total peripheral arteriolar resistance, elevated pulmonary artery pressure, and normal pulmonary arteriolar resistance. An increase in the right ventricular filling pressure was present in five patients. Both total and stroke work of the right and left ventricles were markedly elevated in all patients.

The high cardiac output observed in this group of patients could not be explained on the basis of anæmia, anoxia, or increased oxygen consumption. Water retention and the consequent hypervolæmia known to occur in acute glomerulonephritis would satisfactorily explain the elevation of cardiac output. The normal total peripheral resistance would indicate absence of vasodilatation that usually accompanies other high output states. The combination of hypertension with increased inflow volume in this group of patients produced an elevation of the left ventricular work load far above that present in other high output states of comparable degree, in which the mean arterial pressure is not increased. The writers suggest that the resulting increase in work load was of such a magnitude as to require a greater diastolic volume and, in turn, a significant elevation of the filling pressure. S. J. SHANE

Functional Aortic Stenosis—Resistance to Left Ventricular Outflow without Anatomical Obstruction.

A. G. MORROW AND E. BRAUNWALD: *Circulation*, 20: 181, 1959.

In three patients a functional obstruction to left ventricular outflow was present. In two a significant pressure gradient was shown to exist between the left ventricle and aorta and the obstruction was localized within the left ventricle. At the time of open-heart operation, however, no localized stenotic area could be found and the obstruction was of necessity attributed to systolic narrowing of the ventricular outflow tract resulting from massive muscular hypertrophy, the cause of which was obscure. Such narrowing was subsequently demonstrated in one patient by selective angiocardiography with left ventricular injection of contrast medium. In a third patient, functional aortic stenosis was present after surgical relief of a discrete subvalvular stenosis and regressed during the postoperative period.

The writers emphasize that the recognition of functional aortic stenosis is of considerable importance, since this lesion is at present not amenable to surgical correction and an unnecessary exploration of the ventricle and valve in such a patient is hazardous. The diagnosis may be suggested by certain features present in all patients described. The systolic thrill and murmur are most prominent at the apex and lower left sternal border and less apparent in the aortic area. The thrill is not transmitted to the carotid vessels. Phonocardiography reveals a loud pansystolic murmur at the apex with a softer ejection murmur at the base of the heart. In some cases, however, a typical ejection murmur only is heard. Post-stenotic dilatation of the aorta was not demonstrable in any case. This latter finding is in contrast to congenital subvalvular aortic stenosis.

It would seem that the diagnosis of functional aortic stenosis can be excluded by the demonstration of a pressure difference across the valve and must be suspected when the site of stenosis is shown to be below it. *For this reason complete left heart and aortic catheterization would seem preferable to simple ventricular puncture in the study of patients with aortic stenosis.* Selective left ventricular angiography will probably prove the most definitive diagnostic technique in distinguishing this lesion from the other forms of aortic stenosis and also revealing any accompanying mitral insufficiency.

The persistence of a large pressure gradient after complete relief of a localized subvalvular obstruction can only be attributable to functional aortic stenosis, the hæmodynamic effects of which disappeared during the months after operation. This would indicate that the results of late postoperative studies may be of greatest value in the assessment of operative results.

S. J. SHANE

SURGERY

Prophylactic Postoperative Antibiotics.

J. BARNES *et al.*: *A.M.A. Arch. Surg.*, 79: 190, 1959.

A series of 1007 surgical cases formed two groups for the study of postoperative infections. Without informing the surgeons of the group to which each case belonged, one group was given penicillin and streptomycin from the time of operation for 72 hours and the other group none. The infection rate in 558 cases without antibiotics was 9.8% and in the group of 449 cases with such prophylaxis was 11.4%. Emergency cases were not included in the study. In the antibiotic group 76% of the bacteria cultured from the infections were resistant to the antibiotics used. In the control group only 22% of the bacteria were similarly resistant. BURNS PLEWES

Coexisting Carcinoma and Diverticula of the Colon.

J. L. PONKA, J. DEWITT FOX AND B. E. BRUSH: *A.M.A. Arch. Surg.*, 79: 373, 1959.

In 355 cases of carcinoma of the colon at Ford Hospital, 75 or 21% had associated diverticulosis; in the sigmoid colon the association was 28% and 35 out of 197 cases of cancer had diverticulitis in close association. Sigmoidoscopic examination confirmed the clinical suspicion that carcinoma was present in 57%. Barium enema examination was definitely positive in 45.7% and presumptively correct in 65.7%. Cure rates are proportional to the degree of suspicion of the doctor. Repeated proctoscopic examinations and barium enema studies are necessary in patients with diverticulitis, for they already have the symptoms, indistinguishable from carcinoma, of constipation, bowel change, and abdominal distress.

Surgery should be used more frequently in carefully selected cases of diverticulitis in a population which is aging and destined to have more and more colonic diseases. BURNS PLEWES

Canad. M. A. J.
April 23, 1960, vol. 82

Effect of Pulmonary Resection on Compliance of Human Lungs.

N. R. FRANK, A. A. SIEBENS AND M. M. NEWMAN: *J. Thorac. Cardiovasc. Surg.*, 38: 215, 1959.

Pulmonary compliance, an index of the elastic behaviour of the lungs, is the ratio of the change in volume of the lungs to the change in transpulmonary pressure:

$$\text{Compliance} = \frac{\text{change in lung volume in litres}}{\text{change in transpulmonary pressure in cm. } H_2O}$$

In human beings, intraœsophageal pressure is customarily measured instead of intrapleural pressure, thereby avoiding the danger of puncturing the lungs. The former measurement offers a reliable index of the pressure applied to the surface of the lungs under specified conditions.

Pulmonary compliance was measured in 16 patients before and after partial resection of the lungs. The measurements were made during interrupted breathing while the patients were seated; intraœsophageal pressure was used as an index of the force applied to the surface of the lungs. It was found that the preoperative to postoperative change in compliance, expressed as a percentage of control value, was correlated closely with the number of segments of tissue removed. Almost as close was the correlation between changes in compliance and vital capacity. In general, the functional residual capacity was reduced after operation while intraœsophageal pressure became more subatmospheric. The reduction in compliance was ascribed to reduction in the number of elastic units participating in ventilation.

S. J. SHANE

Tracheotomy in Burns.

J. A. MONCRIEF: *A.M.A. Arch. Surg.*, 79: 45, 1959.

Though thermal injury of the respiratory tract below the larynx is uncommon, irritant inflammation of the tracheo-bronchial tree is frequent and of great significance in the immediate period after burning. Face and neck burns are followed rapidly by œdema and immobilization of the jaws and swelling of the lips with resulting aspiration of vomitus. General anæsthesia becomes risky and difficult in maintaining an adequate airway.

In a review of 1000 cases of burns in a U.S. Army Research Unit, 84 patients had a tracheotomy for either prophylactic or therapeutic reasons. Therapeutic reasons for tracheotomy included respiratory irritation from smoke and fumes, mechanical embarrassment due to local œdema of the larynx or excessive bronchial or tracheal secretion, or associated chest wall injuries. Prophylaxis included a better tracheobronchial toilet in anæsthesia for extensive face burns.

More than half of these patients died. About half had tracheotomies. Most of the deaths were from septicæmia. Immediate relief followed emergency tracheotomy for laryngeal obstruction, though many died of pulmonary œdema or septicæmia later.

There are many complications from tracheotomy tubes that are too long or too short, or are not properly cared for. A block of cartilage should always be removed in doing the operation. The value of the procedure as a prophylactic measure is hard to assess, for it is most often used in the worst cases.

BURNS PLEWES

BOOK REVIEWS

DRIVE STRUCTURE AND CRIMINALITY. Criminobiological Investigation. Hans Walder, Attorney General, Zürich, Switzerland. Translated by Martin W. Webb; edited by Lipot Szondi. 174 pp. Illust. Revised and enlarged. Charles C Thomas, Springfield, Illinois; The Ryerson Press, Toronto, 1959. $8.25.

This is a revised and enlarged edition of an earlier work of the author. Early in the book, it is postulated that "there is a utilizable causal relationship between the specific personality of the offender and the prevailing environment, on the one hand, and the specific offence of which the person is accused on the other". The author, an authority in the fields of criminal law and criminology, and attorney general of the canton of Zürich, develops this thesis with reference to the drive or need pattern of the criminal, as revealed by the Szondi test; the situational factors in the crime; and the crime as defined by the Swiss penal code.

The Szondi test, in the author's experience, is the instrument of choice for such investigations. This test technique involves pictorial selections thought to reveal information regarding the subject's satisfied and unsatisfied needs and his attitudes toward the latter. References to basic Szondi works in English and German are given. One chapter of the book is devoted to test description.

After defining the rationale and scope of his enquiry, the author provides case material illustrating typical drive disorders occurring in various criminal types (thieves, burglars, swindlers, exhibitionists, etc.). This is rounded out by a quite extensive compilation and classification of drive structure types and their crimes. Two cases are subjected to intensive analysis. An appended chapter deals with the criminogenic significance of one class of needs; and 30 selected references are offered, some of which, unfortunately, are untranslated or unpublished dissertations. All in all, the author has brought together a great deal of material, organizing it well.

This book draws attention to a field of enquiry to which not enough work has been devoted on this continent. Would one find the relationships between Szondi responses and criminal acts set out by the author? This is a matter to be determined by appropriate sampling techniques. It awaits further investigation. The author's views in this regard appear less than critical, e.g. "It sometimes occurs—in approximately five cases out of 100—that the readiness to commit a murder is not apparent from the foreground profile, while in the background profile is portrayed the so-called murder syndrome." No precise data of a survey nature are offered to support this contention which involves, among others, the implication that for this type of criminal at least, the test is without error. Regarding the inferred relationship between pictorial choice and drive structure, in some of the cases presented, reference is made to agreement between test interpretation and data derived from other sources, e.g. case material, psychiatric diagnostic reports, and graphological analysis, none of which is particularly searching. The author comments on this issue, noting the hypothetical nature of the inferences and observing that the test has permitted correct "blind" diagnoses and prognoses.

The book should be read with interest by professional workers in forensic psychiatry, psychology, and related disciplines.

INSTRUCTIONAL COURSE LECTURES FOR 1959. Edited by Fred C. Reynolds. 335 pp. Illust. The C. V. Mosby Company, St. Louis, Mo., 1959. $16.00.

This well-known volume, now in its sixteenth consecutive year, maintains the high standard of publication and presentation for which it is noted. The subject matter covers widely varied aspects of orthopædic surgery and is a commentary on present-day thinking.

Not all topics discussed at the actual meeting are included and, naturally, the selection cannot please all readers. A noteworthy opening feature is a section on athletic injuries, ankle injuries being especially well dealt with. Description of the anatomy of the hand has been prominent of late in other publications. Its present inclusion, however, is entirely justified by a clear presentation with excellent photographic demonstrations. A section on foot problems follows, but discussion of the operative treatment of club-feet lacks clarity in places. The treatment of valgus feet with particular reference to subtalar extra-articular arthrodeses is, however, clearly and comprehensively reviewed.

In the spine section, the subject of scoliosis is presented quite well but is confusing here and there. A statistical report on the follow-up of over 1000 backs operated on for disc disease supports those who advocate spinal fusion following discotomy. The difficult problem of the disposal and future of the low-back cripple receives due attention.

The pathological and clinical aspects of osteomyelitis are discussed in a very good paper—one of a group on miscellaneous subjects.

The last section deals briefly with elbow fractures and gives a good bibliography. This is followed by a symposium on the treatment of acute fractures of the femoral neck by intramedullary prosthesis replacement arthroplasty. In general, little encouragement is given for this form of treatment and the outlook seems very glum. However, the slightly over-enthusiastic attitude of Dr. Austin Moore justifiably lightens the final pages.

This volume can be as highly recommended as its predecessors.

WORK AND THE HEART. Edited by Francis F. Rosenbaum and Elston L. Belknap, Marquette University School of Medicine, Milwaukee, Wis. 537 pp. Illust. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, 1959. $12.00.

This volume is the report of the First Wisconsin Conference on Work and the Heart. The sponsors recognized that knowledge about the effects of exercise and stress on the heart is "inadequate, confused and contradictory". This conference was an attempt to consolidate information on the subject and more particularly to expose the areas of ignorance and to suggest lines of investigation for the future. In this it has succeeded admirably.

The five sections deal with basic physiology, clinical physiology, pathology, work classification and workmen's compensation. The formal presentations are followed by summaries of the panel discussions. The topics include the contractile proteins, cardiac output, measurement of cardiac performance, effects of emotion and exercise, sudden death from coronary disease, work classification units, and the relation of cardiac disease to workmen's compensation.

The excellence of these various papers can be appreciated only by careful perusal. Everyone interested in industrial medicine or in cardiology should read all or most of this outstanding publication.

HÆMORRHAGIC NEPHROSO-NEPHRITIS. A. A. Smorodintsev, V. G. Chudakov and A. V. Churilov. Translated from the Russian by Catherine Matthews. 124 pp. Illust. Pergamon Press Inc., New York, 1959. $9.00.

The disease under consideration is an interesting renal disorder unfamiliar to Western physicians. The authors present a thorough study of what they have reason to think is a widespread viral infection, affecting capillaries, the nervous system, the liver and in particular the kidneys. The disease has occurred in epidemic form in various parts of Asia. Many observations concerning its etiology, epidemiology, clinical picture, pathological features and treatment are brought together in this monograph. The sections on therapy mention some measures of questionable value, such as the administration of calcium chloride to diminish the risk of hæmorrhage by increasing the stability of vessel walls and the prescribing of ascorbic acid despite lack of evidence of a deficiency of the vitamin.

The book should interest physicians who are students of renal diseases. It provides an example of medical writing and a glimpse of medical practice in modern Russia. Should the disease spread to the West, the book would be in great demand.

RECENT PROGRESS IN OXYTOCIN RESEARCH. B. Berde, Pharmacological Laboratory, Sandoz Ltd., Basle, Switzerland. American Lecture Series. 110 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $5.25.

The history of oxytocin is reviewed in this small volume with particular emphasis on recent experimental and clinical studies. The chemical structure of oxytocin and its production, release, action and fate are discussed in a comprehensive manner. The many important developments in all these fields are related to earlier work in an interesting and easy way. In short, the reader is given a "bird's eye view" of current fundamental knowledge of oxytocin. Because of the rapid progress which has been made in the subject under review, such a book is of potential interest to a wide medical audience. The general practitioner, the obstetrician, the internist, the physiologist, and the pharmacologist could profit and derive pleasure from reading this monograph.

DONNEES ACTUELLES SUR LA PHYSIOLOGIE ET LA PATHOLOGIE CLINIQUE DES PARATHYROIDES. (Present data on physiology and clinical pathology of the parathyroids). B. Courvoisier and others. 94 pp. Illust. Benno Schwabe & Co., Basle/Stuttgart; Intercontinental Medical Book Corporation, New York, 1959. $2.25.

This very concise book represents an attempt by the author to summarize some of the more recent thoughts on calcium and phosphorus metabolism in relation to the parathyroid hormone and to diseases of the parathyroid glands. The author reviews some of the experiments on parathyroid hormone action. He discusses the values of such tests as % TRP and calcium loads and also presents some of his own experience with these tests, applied to the differential diagnosis of parathyroid disease. There is a short clinical discussion of hyperparathyroidism and hypoparathyroidism in which the author emphasizes the bony manifestations that may be detected radiologically in hypoparathyroidism.

This book is definitely not directed to the specialist in parathyroid disease or in calcium and phosphorus metabolism. Many investigators will disagree with the author's opinion on the diagnostic value of such tests as % TRP and calcium infusions in parathyroid disease.

Canad. M. A. J.
April 23, 1960, vol. 82

EVALUATION OF CHANGES ASSOCIATED WITH PSYCHIATRIC TREATMENT. Marvin Reznikoff and Laura C. Toomey. 132 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $5.00.

This small but meaty book is not one to be read by persons seeking enlightenment on either the various methods of psychiatric treatment or the effectiveness of these methods. Originally intended as "investigations of changes in *psychotherapy*" (reviewer's italics), the authors later broadened their intent but without notably broadening their content. Moreover, the word "evaluation" in the title refers to evaluations and critiques of methodologies of past studies, rather than to evaluations of specific claims. Thus the book is primarily for researchers in the field, rather than for the general reader seeking to discover just how effective present methods of psychotherapy are.

Considered as such, this volume contains a wealth of data. The authors first consider some of the theoretical and practical problems encountered in such research, with respect to research design, methods of control selection of subjects, etc., and illustrate this section by a detailed analysis of the pitfalls in the Eysenck controversy (the claim that psychotherapy has little better than "chance" effect). Next the authors consider a number of specific studies grouped in terms of clinical judgments, psychological tests, physiological measures, content analysis and intra-individual measures. While by no means exhaustive, and in some cases disappointingly meagre (e.g. in physiological measures), this last section is quite representative of the main currents of present research in individual psychotherapy. In summary, then, this book will spare the neophyte in psychiatric research many hours of searching through the literature.

Perhaps, however, the main interest of this tiny volume (and others of its kind recently published) is the unintentional bench-mark that it places on the course of psychiatric research; the methodology, the focus of study and the division of labour for future research in this area are now apparent.

Psychiatry, like other branches of medicine, evolved primarily as an empirical science, paying little attention to problems of methodology, techniques, and the evaluation of different approaches within the discipline. However, as newer methods of physical and pharmacological treatment made inroads on the grosser pathologies, psychiatry began to pay more and more attention to its dictum that the *total* individual should constitute the focus of treatment. Almost immediately, however, investigators were confronted by the inadequacies of their established concepts of "normality" when applied to broader aspects of the human condition.

It was in an attempt to arrive at some universally accepted criterion of normality, as well as to establish its claim to "all knowledge" of the human condition as its province, that psychiatry began to work in closer and closer liaison with psychology and the social sciences, thus broadening even further the content of its studies. The outcome of this attempt is perhaps well reflected in the recent *American Handbook of Psychiatry* with its chapters on topics as diversified as the family, the community, juvenile delinquency, cybernetics, philosophy, religion, etc., etc. It was this same catholicity of intent which led Stanley Cobb to quip, "Many modern psychiatrists are so busy trying to puzzle out how to study 'the patient as a whole' that they have to call in a neurologist to analyze an aphasic disorder."

However, the alliance with the social sciences had other important consequences. Psychology, for example, as the step-child of philosophy and physiology was intent on applying the rigorous scientific methodology of the latter parent to the questions of the former. Consequently it was not long before it began to be critical of the empirical methods employed in psychiatric practice and research. Faced with its own problems of expansion and impressed by the research sophistication of psychology, psychiatry was only too willing that psychologists should take increasing responsibility for research in the field.

Thus it is that the authors are both psychologists at the Institute of Living at Hartford, Connecticut. Moreover, the great bulk of studies cited were conducted by psychologists and other social scientists. Such evidence heightens the impression that this division of labour will continue.

Such a division has pitfalls, however. The rigorous controls and precision demanded by a properly scientific design are often at variance with the flexibility of approach demanded by clinical practice. Not only are there questions of ethics involved (e.g., the use of non-treated patients as controls), but the clinician must himself become as much an object of study as the patient, since the evidence is all too clear that the expectations and perceptions of the clinician play a significant part in the outcome. Consequently the sobering thought left by this book is that we need to know much more about the *process* of psychotherapy and the effects of both the practitioner and the researcher on this process before we can make significant progress towards evaluating the *effectiveness* of the process. Such questions promise to be the major considerations of psychiatric research in the immediate future.

HANDBUCH DER TUBERCULOSE: Band I (Manual of Tuberculosis: Volume I). H. Bloch and others. Edited by J. Hein, H. Kleinschmidt and E. Uehlinger. 832 pp. Illust. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1958. $42.40.

The present volume is the first of a series of five in which the editors attempt to give a complete description of our present-day knowledge of tuberculosis. The book is written in German, but is international in origin. The first volume contains, among others, chapters on the history of tuberculosis by Löffler (Switzerland), bacteriology and immunology by Suter and Bloch (U.S.A.), epidemiology by Redeher (Germany), and sources and dissemination of the infection by Hedvall (Sweden). Each chapter has an extensive up-to-date bibliography of the world literature.

A detailed discussion of this volume would be beyond the scope of a short review. The *Handbuch* is an excellent reference work and can be recommended to all physicians interested in the subject. Print and illustrations are of the highest quality.

The further volumes will deal with the pathological anatomy, medical and surgical aspects of pulmonary tuberculosis, extrapulmonary tuberculosis and epidemiology.

PULMONARY CIRCULATION. Edited by Wright R. Adams and Ilza Veith. 316 pp. Illust. Grune and Stratton, London and New York, 1959. $4.50.

An international symposium on pulmonary circulation was held in Chicago in March 1958, at which a group of active investigators in this field were invited to express their concepts, present results of recent researches and discuss experiences with one another. The present book records their program.

The program consisted of five half-day sessions—one on physiology of pulmonary circulation, another on pathology and one each on pulmonary circulation in primary lung disease, in congenital heart disease and in acquired heart disease. The book is similarly divided into these various sections. The majority of the 30 papers presented were from the U.S.A. but other countries participated, including England, Scandinavia, Canada and Mexico. These papers are reproduced along with the discussion that occurred.

It is obvious in reading the book that many of the workers have spent a good deal of time and effort in various ingenious research methods in an attempt to clarify ideas or present new facts. Many of the papers are excellent and the discussion is concise and pertinent.

Although the volume does not cover all phases of the subject or all diseases in which the pulmonary circulation is involved, it contains much of the recent work in the field and should appeal to all those who were unable to attend the symposium, particularly to cardiologists, cardiac surgeons, those whose primary interest is diseases of the chest, and internists in general.

THE CLINICAL SYNDROME OF DIABETES MELLITUS. John Lister. 234 pp. Illust. H. K. Lewis & Co. Ltd., London, England, 1959. $3.80 approx.

In this book, Dr. Lister conveys his enthusiasm for the energetic treatment of diabetes mellitus to the reader. It is a book written for doctors who are not full-time diabetic specialists and for medical students.

In the preface, the author points out that the emphasis is mainly clinical with the aim of presenting the many clinical variations of the syndrome and the details of diabetic management. There is a need for a book which is intermediate in complexity between standard medical textbooks and the comprehensive volumes on diabetes, such as Joslin's and Duncan's textbooks. Dr. Lister fills this need.

In spite of the clinical emphasis the author has managed to cover the more fundamental physiological, biochemical and endocrinological aspects of the diabetic syndrome in a lucid fashion.

The book is divided into three parts. The first is concerned with diagnosis and treatment; the second, with the complications and associated conditions, such as pregnancy, tuberculosis and surgery, in diabetic patients; and the third with the medico-social aspects of the disease. These aspects of the disease are presented in a very readable fashion; the only shortcoming of the book is the chapter on oral hypoglycæmic agents, which considers carbutamide and tolbutamide only very briefly. However, when the manuscript of the book was being prepared these drugs were still in the stage of clinical investigation.

The mainstay of diabetic treatment is still insulin, diet, education and careful follow-up of the patient. These principles are presented clearly and enthusiastically in a readable fashion.

COMMUNITY MENTAL HEALTH. Margaret C.-L. Gildea, Washington University School of Medicine. 169 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $5.50.

This book describes two specific projects: (1) a school-centred mental health service and (2) a program of mental health education by lay people. These programs were developed over the years 1947-1959 in and around St. Louis, Missouri.

By using a simple but fairly practical method of classifying the emotional disturbances of schoolchildren, very severely disturbed children were screened out for intensive clinical help. To treat persistent but moderately severe problems the school-centred service was set up. These children came from homes where at least one parent was able to make an effort to understand and improve the situation.

The method consisted in regular weekly meetings with mothers under an experienced group-therapist. Two such groups are described in detail and this is very interesting reading. The results were encouraging in that 80% of the children showed marked improvement. Groups which were unsuccessful are reported. A careful study of the reasons for failure is very enlightening.

The second project was planned to help normal children, and children with mild degrees of emotional disturbance. Methods of recruiting and training lay-leaders are described. Again an analysis of success and failure will prove quite fascinating reading for anyone interested in parent education and community mental health programs.

This little book would not appeal to the busy doctor unless he were very interested in the emotional development of children, and the prevention and treatment of behaviour problems. It would be a valuable addition to the library of any professional or lay worker in the field of community mental health.

PROGRESS IN MEDICAL VIROLOGY. Vol. 2. Edited by E. Berger, Basel, Switzerland, and J. L. Melnick, Houston, Texas, U.S.A. 234 pp. Illust. Hafner Publishing Company, Inc., New York, 1959. $10.25.

This volume is of great value for the research worker or teacher in virology. The subjects dealt with are chemotherapy of virus infections, electron microscopy of viruses in thin sections of cultured cells, metabolism of virus-infected cells, properties of AB-IV-Coxsackie A7 group of viruses, salivary gland viruses of man and animals, and a review of viruses of the respiratory tract. Each author of these sections is an international authority on his subject, and the products are therefore authoritative articles on these important aspects of virology. The bibliographies are remarkably complete, and the volume as a whole will prove invaluable to workers in this field.

ANTIBIOTICS IN MEDICINE

The issue of the *British Medical Bulletin* dealing with Antibiotics in Medicine was referred to in our review (March 19, 1960, page 37) as being available at the Oxford University Press, Toronto. We are now informed that orders for this *Bulletin* should be sent to the British Council, 65 Davies St., London, W.1.

Books Received

Books are acknowledged as received, but in some cases reviews will also be made in later issues.

Klinische Physiologie (Clinical Physiology). W. A. Müller. 118 pp. Illust. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1960. $5.50.

Ring the Night Bell. The Autobiography of a Surgeon. Paul B. Magnuson. 376 pp. Little, Brown and Company, Boston and Toronto, 1960. $5.50.

Emergencies in Medical Practice. Edited by C. A. Birch. 751 pp. Illust. 6th ed. E. & S. Livingstone Ltd., Edinburgh and London; The Macmillan Company of Canada Limited, Toronto, 1960. $7.65.

Medullary Sponge Kidney. A Roentgenologic, Clinical, Histopathologic and Biophysical Study. R. Ekstrom, B. Engfeldt, C. Lagergren and N. Lindvall. 73 pp. Illust. Almqvist & Wiksell, Stockholm, Sweden, 1959. $3.40 approx.

A Biochemical Approach to Pathology. M. J. R. Dawkins and K. R. Rees. 128 pp. Illust. Edward Arnold (Publishers) Ltd., London, England; The Macmillan Company of Canada Limited, Toronto, 1959. $3.00.

The Medical Annual. A Year Book of Treatment and Practitioners' Index. Edited by R. B. Scott and R. Milnes Walker. 620+19 pp. Illust. 77th Year. John Wright & Sons Ltd., Bristol, England; The Macmillan Company of Canada Limited, Toronto, 1959. $7.15.

The Antibiotic Saga. H. Welch and F. Marti-Ibanez. 150 pp. Medical Encyclopedia Inc., New York, 1960. $3.00.

Fluoridation. Errors and Omissions in Experimental Trials. P. R. N. Sutton. 83 pp. Illust. Melbourne University Press, Carlton, Australia; The Macmillan Company of Canada Limited, Toronto, 1959. $1.45.

A Catalogue of the Portraits and other Paintings, Drawings and Sculpture in the Royal College of Surgeons of England. W. LeFanu, Librarian of the College. 118+52 pp. Illust. E. & S. Livingstone Ltd., Edinburgh and London; The Macmillan Company of Canada Limited, Toronto, 1960. $5.00.

At Your Best for Birth (And Afterwards). E. Montgomery. 59 pp. Illust. John Wright & Sons, Ltd., Bristol, England; The Macmillan Company of Canada Limited, Toronto, 1959. $0.95.

Infant Foods and Feeding Practice. A Rapid Reference Text of Practical Infant Feeding for Physicians and Nutritionists. H. F. Meyer. 332 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $11.00 approx.

May and Worth's Manual of Diseases of the Eye. T. K. Lyle and A. G. Cross. 748 pp. Illust. 12th ed. Baillière, Tindall & Cox, London, England; The Macmillan Company of Canada Limited, Toronto, 1959. $7.65.

Practical Proctology. L. A. Buie. 737 pp. Illust. 2nd ed. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $25.00 approx.

Surgery of Repair as Applied to Hand Injuries. B. K. Rank and A. R. Wakefield. 284 pp. Illust. 2nd ed. E. & S. Livingstone Ltd., Edinburgh and London; The Macmillan Company of Canada Limited, Toronto, 1960. $7.65.

Atlas der Gynäkologischen Operationen (Atlas of Gynæcological Operations). O. Käser and F. A. Iklé. 451 pp. Illust. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1960. $35.25.

Cardiac Auscultation, Including Audio-Visual Principles. J. S. Butterworth, M. R. Chassin, R. McGrath and E. H. Reppert. 102 pp. Illust. 2nd ed. Grune & Stratton, New York and London, 1960. $6.25.

Institutional Neurosis. R. Barton. 56 pp. Illust. John Wright & Sons Ltd., Bristol, England; The Macmillan Company of Canada Limited, Toronto, 1959. $1.45.

The Modern Treatment of Asthma. With Special Reference to Gold Therapy. L. Banszky. 175 pp. 2nd ed. John Wright & Sons Ltd., Bristol, England; The Macmillan Company of Canada Limited, Toronto, 1959. $3.60.

Your Health and Your Wealth. By a Doctor. 139 pp. John Wright & Sons Ltd., Bristol, England; The Macmillan Company of Canada Limited, Toronto, 1959. $1.30.

Physiology of the Retina and Visual Pathway. G. S. Brindley. 298 pp. Illust. Edward Arnold (Publishers) Ltd., London, England; The Macmillan Company of Canada Limited, Toronto, 1960. $6.00.

Modern Treatment Yearbook 1960. Edited by Sir Cecil Wakeley. 310 pp. Illust. 26th ed. Baillière, Tindall & Cox, Ltd., London, England; The Macmillan Company of Canada Limited, Toronto, 1960. $5.60.

Anatomy. A Regional Study of Human Structure. E. Gardner, D. J. Gray and R. O'Rahilly. 999 pp. Illust. W. B. Saunders Company, Philadelphia and London, 1960. $15.00.

Human Biochemical Genetics. H. Harris. 310 pp. Illust. Cambridge University Press, London, England; The Macmillan Company of Canada Limited, Toronto, 1959. $6.35.

ASSIGNMENT OF LEASE AND SALE OF EQUIPMENT

We are Executor of the Estate of a General Practitioner who had an established practice at Wetaskiwin, Alberta.
There are fully equipped office facilities for use of two or more doctors which were specially planned for use as a Doctors' office. The lease on the premises will expire on 14th December, 1962.
Additional space, if required, will be available about 1st November next which would give occupancy of the whole building and provide ideal quarters for the operation of a clinic.
Wetaskiwin is a thriving city, population approximately 5,700 located 40 miles south of Edmonton with a well populated surrounding district. A hospital is located within two blocks of office.
This location provides excellent opportunity for establishment of a successful practice.

For further information:

The Royal Trust Company,
10039 - Jasper Avenue,
Edmonton, Alberta.

CITY MEDICAL CORRESPONDENCE COLLEGE

SPECIALISES IN POSTAL TUITION FOR ALL POST GRADUATE EXAMINATIONS INCLUDING M.D., F.R.C.S., M.R.C.P., D.A., D.T.M., D.O., D.P.M., D.C.H., etc. PLEASE STATE QUALIFICATION IN WHICH YOU ARE INTERESTED:

THE REGISTRAR,
56 Cannon Street, London, E.C.4, England.

NAME.....

ADDRESS.....

.....

I AM INTERESTED IN.....

POST GRADUATE STUDY

For Canadian and U.S.A. Practitioners

Are you preparing for any Medical, or Surgical Examination?

Send Coupon below for valuable publication

"GUIDE to MEDICAL EXAMINATIONS"

PRINCIPAL CONTENTS

The F.R.C.S. England and Edinburgh.
The F.R.C.P. & S. of Canada and Certification Exams.
The M.R.C.P. London and Edinburgh.
Diploma in Anæsthetics.
The Diploma in Tropical Medicine.
Diploma in Ophthalmology.
Diploma in Psychological Medicine.
Diploma in Child Health.
Diploma in Physical Medicine.
Diploma in Public Health.
Diploma in Pathology.

You can prepare for any of these qualifications by postal study at home and come to Great Britain for examination. We specialize in Post-graduate tuition. Courses for all Canadian and U.S.A. qualifications.

THE SECRETARY
MEDICAL CORRESPONDENCE COLLEGE
19 Welbeck Street,
London, W.1.

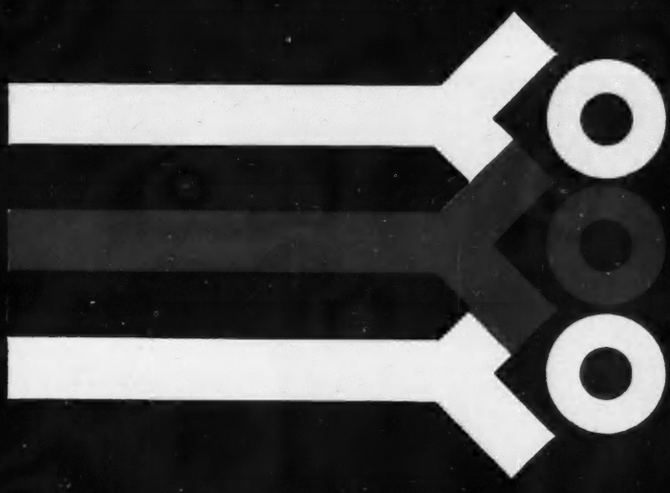
Sir,—Please send me a copy of your "Guide to Medical Examinations" by return.

Name .....

Address .....

Examinations in which interested.....
C.M.A.

'Darenthin'



a major break-through
in the treatment of

hypertension

'Darenthin'* BRAND

Bretylium Tosylate Tablets of 200 mg. (Scored).

TRADE MARK

BURROUGHS WELLCOME & CO. (CANADA) LTD. Montreal

MEDICAL NEWS *in Brief*

(Continued from page 891)

MALARIA ERADICATION IN THE AMERICAS

In 1954 a continent-wide campaign was undertaken to eradicate malaria in the Americas, This campaign was begun because those nations and territories that had eradicated the disease within their own borders — Barbados, Chile, Martinique, Puerto Rico and the United States — plus those where malaria had never been present or had disappeared without eradication—Canada, Uruguay and 11 Island Territories — wished to protect themselves from re-infection, while the remainder wanted to follow their example in ridding themselves of the disease. At that time 96,000,000 persons still lived in areas of the New World infected with malaria. Though the Americas had to begin from scratch in a field pregnant with obstacles, since the campaign began malaria has been completely cleared from lands where 7,000,000 people live. In other areas inhabited by 2,000,000 persons, no cases have been reported for from one to three years. This leaves 87,000,000 living in areas where anti-anopheline measures are still to be completed. It is comforting to realize that eradication is possible; it has worked and will work whenever the campaign is pushed with the requisite diligence, public support and imagination.

—

HAZARDS OF TATTOOING

The hazards of tattooing are discussed by Lieutenant Richard Graham Davis, M.C., U.S.N., in the *U.S. Armed Forces Medical Journal* March 1960, page 261. Apparently the frequency of tattooing is difficult to determine in the population as a whole. Amongst the service personnel probably the incidence is highest, but even here it varies considerably. The special circumstances of prolonged detention in prisoner-of-war camps were associated with outbursts of tattooing as a fad to relieve boredom. However, there are definite medical complications which are significant in number and of special interest to medical officers.

Serious complications from tattooing are fairly rare. It is only in the last century that the first authentic report of its medical aspects was made. Since then, however, the literature has become rather extensive.

The immediate result of tattooing is simply the normal inflammatory response of the skin to multiple small puncture wounds, and this inflammatory response should subside fairly soon. The most likely complication of the tattooing is secondary infection and it is rather striking that considering the circumstances under which it is usually, or very often, done, there are not more secondary infections than do occur. However, this complication has probably become lessened on account of the recognized importance of cleanliness and stricter governmental control.

As regards nonpyogenic infections the literature contains a long list of diseases transmitted by means of tattooing. Syphilis was the first disease noted (in 1853) to be transmitted in this way. This

strengthens
fragile capillaries
in internal bleeding

capillary hemorrhage
in duodenal ulcer

. . . associated with abnormal capillary permeability and fragility in

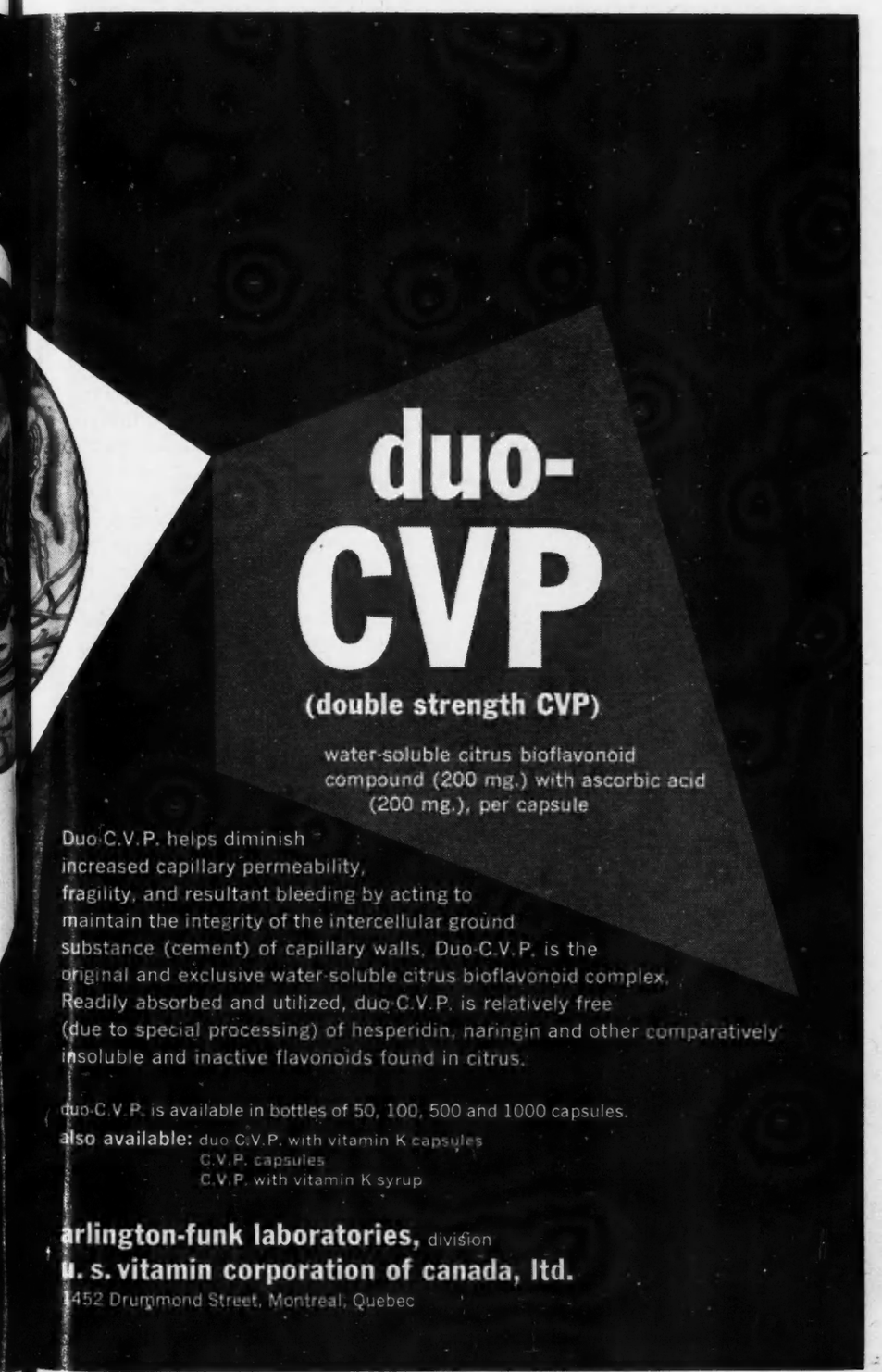
peptic ulcer
ulcerative colitis
chronic nosebleed
purpura
(nonthrombocytopenic)
hemorrhagic cystitis
ecchymoses
menorrhagia
habitual and threatened abortion

occurred when the tattooer with luetic mucous patches in the mouth used his saliva to moisten needles or pigments, but instances of this transmission of syphilis have been reported only rarely since the early years of this century. However, in 1935 the incidence of positive Wassermann reactions in a group of 265 tattooed Japanese iron workers was reported as being significantly higher than amongst non-tattooed similar workers.

Tuberculosis also has been known to be transmitted in this way.

A more common complication of tattooing is the development of sensitivity to the injected pigments, especially mercury, which is the basis of almost all the red used in tattooing. There are other preparations such as red ochre, cadmium selenide, madder, sandalwood, etc., but usually the red mercuric sulfide is employed and as may be expected the incidence of sensitivity to this is fairly high. The other pigments are of low antigenic potential and rarely sensitize.

As to removal of the tattoo marks, there seems to be no end to the methods and materials that have been advocated at one time or another, some being very heroic in nature such as the self-application of strong caustics. Where the tattoo is extremely extensive it is almost impossible to remove it by surgical means, but in favourable and not too large areas, the method of choice is surgical excision.


duo-
CVP
(double strength CVP)
water-soluble citrus bioflavonoid
compound (200 mg.) with ascorbic acid
(200 mg.), per capsule
Duo-C.V.P. helps diminish
increased capillary permeability,
fragility, and resultant bleeding by acting to
maintain the integrity of the intercellular ground
substance (cement) of capillary walls. Duo-C.V.P. is the
original and exclusive water-soluble citrus bioflavonoid complex.
Readily absorbed and utilized, duo-C.V.P. is relatively free
(due to special processing) of hesperidin, naringin and other comparatively
insoluble and inactive flavonoids found in citrus.
duo-C.V.P. is available in bottles of 50, 100, 500 and 1000 capsules.
also available: duo-C.V.P. with vitamin K capsules
C.V.P. capsules
C.V.P. with vitamin K syrup
arlington-funk laboratories, division
u. s. vitamin corporation of canada, ltd.
1452 Drummond Street, Montreal, Quebec

MONKTON, ONTARIO IS LOOKING FOR A DOCTOR

The Lions Club of Monkton, Ont., has been looking for a doctor to settle in that community. The village proper has a population of just under 500, coupled with a farm population of an additional 1000 persons within a radius of five miles. The area is considered prosperous.

The village itself is populated with a friendly type of people, many of German origin, and there is a useful and busy community life. There are three Protestant churches, Lutheran, Presbyterian and United. A Roman Catholic church is located some three miles away and an Anglican church some five miles away. Various communities with excellent shopping facilities and services are within reach: Kitchener, 35 miles; Stratford, 25 miles; Mitchell, 12 miles; Listowel, 10 miles. Excellent hospitals are in close range at Listowel, Stratford, Kitchener and London. The income potential is good and inquiries should be directed to Mr. R. J. Blackwell, Secretary, Monkton Lions Club, Monkton, Ontario.

NEW SMALL RESUSCITATOR IS OF WIDE INTEREST

A new lightweight resuscitator called the Pulmonator has been introduced by Canadian Liquid Air Company. Not bigger than a football and weighing less than 1 lb., it permits inflation of the lungs intermittently.

Consisting of a specially designed self-inflating rubber bag with valve and face piece, the Pulmonator is operated by gentle manual compression. It is designed primarily to supply air, but it may be connected quickly to a cylinder of oxygen

(Continued on page 30)

MEDICAL NEWS *in brief*

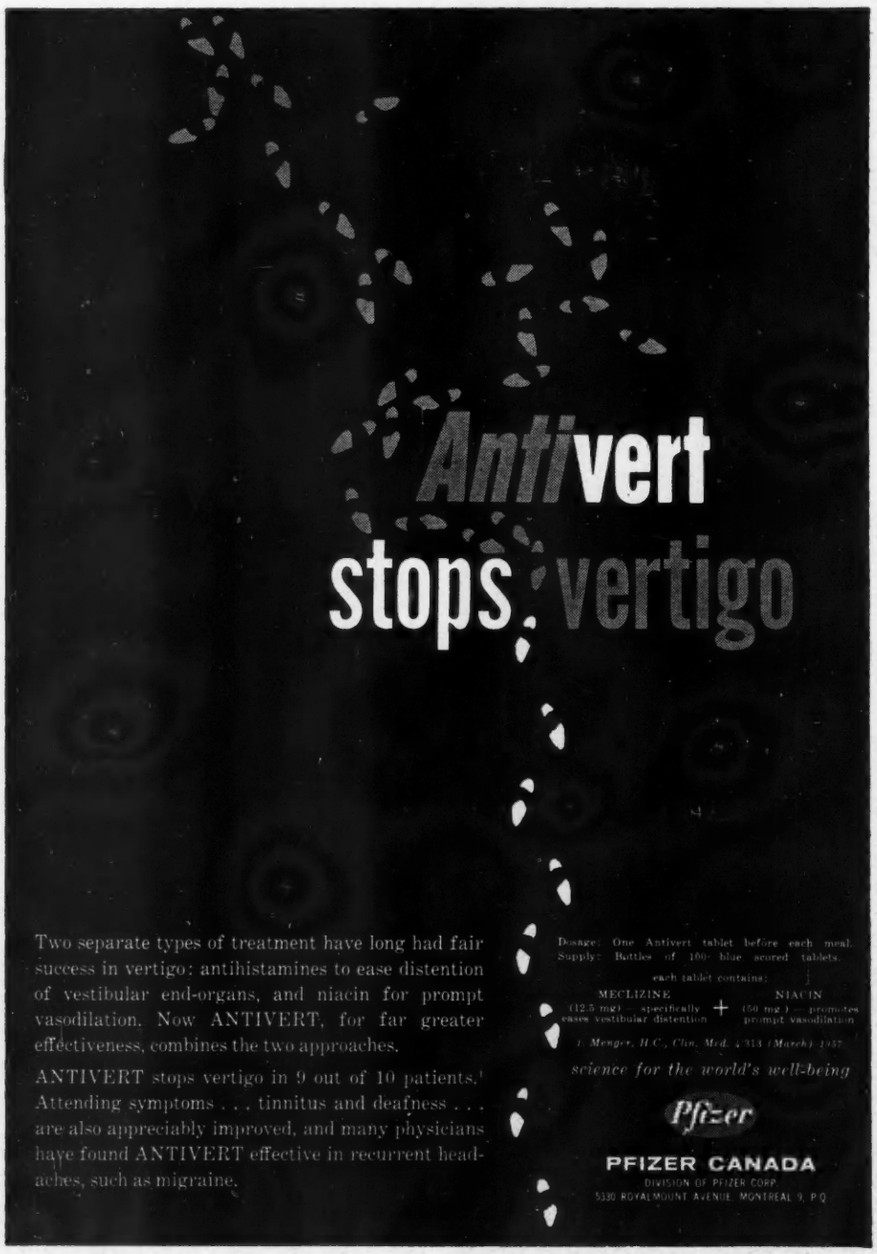
(Continued from page 29)

by means of an inlet at the end of the bag.

It will deliver 1200 c.c. to 1400 c.c. of air with each moderate compression and as much as three litres with maximum compression. The bag is equipped with a substantial face mask and a special foam plastic liner which automatically expands the bag after each compression.

The most important component of the Pulmonator is the modified, 90° Lewis-Leigh non-rebreathing valve which prevents the escape of air during positive pressure inhalation and also acts as the avenue for the escape of exhaled air. The one-way inlet valve also incorporates an oxygen nipple whereby oxygen up to 40-45% of the total mixture may be added, attaching the nipple to a suitable oxygen supply.

The Pulmonator is packaged in a durable vinyl bag with zipper and grommet for hanging the unit in a readily accessible location.


Antivert
stops vertigo
Two separate types of treatment have long had fair success in vertigo: antihistamines to ease distention of vestibular end-organs, and niacin for prompt vasodilation. Now ANTIVERT, for far greater effectiveness, combines the two approaches.
ANTIVERT stops vertigo in 9 out of 10 patients.[1] Attending symptoms . . . tinnitus and deafness . . . are also appreciably improved, and many physicians have found ANTIVERT effective in recurrent headaches, such as migraine.
Dosage: One Antivert tablet before each meal.
Supply: Bottles of 100 blue scored tablets.
each tablet contains:
MECLIZINE
(12.5 mg.) — specifically eases vestibular distention
+
NIACIN
(50 mg.) — promotes prompt vasodilation
1. Menger, H.C., Clin. Med. 4:313 (March) 1957
science for the world's well-being
Pfizer
PFIZER CANADA
DIVISION OF PFIZER CORP.
5330 ROYALMOUNT AVENUE, MONTREAL 9, P.Q.

COMMITTEE ON ADDICTION-PRODUCING DRUGS, W.H.O.*

In its Tenth Report, the Expert Committee on Addiction-Producing Drugs recommended that eight new substances derived from different chemical groups and all having morphine-like effects should be subject to international control. These substances are allylprodine, benzethidine, furethidine, levophenacylmorphan, metazocine, norlevorphanol, phenazocine and piminodine.

The Committee felt that the fundamental criterion for the establishment and degree of control is the extent to which drug-induced behavioural disturbances are a risk to the community, for neither the chemical structure *per se* nor any definition, however descriptive, can be a complete guide indicating which substances should be placed under control. Consequently, there is a need for research along various lines in the field of drug addiction. In particular, to help the World Health Organization in carrying out its functions, the Committee must have at its disposal the results of basic and applied research in this field. But so far sufficient support has not been forthcoming for such investigations. The Committee therefore strongly urged that research on drug addiction should be strengthened and expanded, since it continues to be a serious international public health problem.

*Expert Committee on Addiction-Producing Drugs. Tenth Report. *World Health Organization: Technical Report Series*, No. 188, 1960; 16 pages. Price: 1s. 9d., $0.30, or Sw. fr. 1.–. Also published in French and Spanish.

ORAL TREATMENT OF DIABETES

Azerard and Lubetzky *et al.* (*Presse méd.*, 67: 271, 1959), relying on the animal experimentation of Stern, used a new hypoglycæmic drug called *Glucophage* (N-N-dimethyl-diaguanide) in the treatment of 88 diabetics. This drug is presented in tablets of 500 mg. The initial dose is two to three grams given daily in three or four fractions each of which is preferably taken in the middle of a meal. Maintenance dose is 500 to 1500 mg. a day. Doses of 5000 mg. did not produce results which lower doses had failed to secure. Evaluation of results was based on dura-

(Continued on page 33)

MEDICAL NEWS *in brief*

(Continued from page 30)

tion and severity of the disease, and judged according to the age of the patient and his insulin requirement. Results were considered good when the urine remained free of sugar and glycæmia did not exceed 160 mg. % over any 24-hour period. Adequate results were those obtained when the urine sugar was substantially reduced, the blood sugar remained below the permissible level or when insulin requirements were considerably diminished. Otherwise the results were considered insufficient. Of this series of 88 patients, good results were secured in 34 (38.6%), adequate results in 35 (39.8%) and unsatisfactory results in the remainder. Hypoglycæmic reactions were noted in 69 cases (74.8%). Among the various factors influencing the therapeutic efficacy of the drug, the following were noted: age of the patient (successful results are less likely to be obtained below the age of 40) and onset of illness (the longer the duration of the illness, the less satisfactory the results proved to be). As regards the severity of the disease, the mild diabetes of obese patients responded better to *Glucophage* than the severe form with a tendency towards acidosis. Successful results were obtained five times more frequently in patients not receiving insulin than in those requiring insulin. The only side effects noted were nausea, anorexia with occasional vomiting and diarrhœa in a small minority of patients. The clinical impression derived from this trial is that the "spectrum" of the diaguanides seemed wider in the treatment of diabetes than that of the drugs derived from sulfonamides.

JAGUAR
MARK IX

THE MOST EXPENSIVE OF ALL JAGUARS, BUT AT A PRICE LESS than you would expect. Singularly elegant styling with disc brakes and power steering, and a wealth of power provided by the new 3.8 litre XK engine. This sedan is designed to satisfy the most demanding connoisseur.

SEE YOUR JAGUAR DEALER

Factual Clinical Data: Male, 65, with dislocated shoulder; patient in great pain. Fifteen minutes after administration of 10 cc. of ROBAXIN Injectable, dislocation reduced on first attempt, and patient was able to move arm easily. Photographs used with patient's permission.

For prompt, prolonged, pain-free relaxation of skeletal muscle spasm— without drowsiness...

Robaxin®

Robins

Methocarbamol 'Robins' U.S. Pat. No. 2770649

ROBAXIN Injectable: for relaxation of painful spasm within minutes.

ROBAXIN Tablets: for initial relief, or to maintain relaxation originally induced by ROBAXIN Injectable. Virtually free from adverse side effects, including drowsiness.

Ten published studies show ROBAXIN Injectable and ROBAXIN Tablets beneficial in 91% of cases.[1-10] Literature available to physicians on request.

SUPPLY: ROBAXIN Tablets, 0.5 Gm. (white, scored) in bottles of 50 and 500.

ROBAXIN Injectable, each ampul containing 1.0 Gm. of methocarbamol in 10 cc. of sterile solution.

A. H. ROBINS CO. OF CANADA, LTD., Montreal, Quebec

Making today's medicines with integrity . . . seeking tomorrow's with persistence

REFERENCES: 1. Carpenter, E. B.: Southern M. J. 51:627, 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. Grisolia, A., and Thomson, J. E. M.: Clin. Orthopaedics 13:299, 1959. 4. Hudgins, A. P.: Clin. Med. 6:2321, 1959. 5. Lewis, W. S.: California Med. 90:26, 1959. 6. O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. 7. Park, R. W.: J.A.M.A. 167:165, 1958. 8. Plumb, C. S.: Journal-Lancet 78:531, 1958. 9. Poppen, J. L., and Flanagan, M. E.: J.A.M.A. 171:298, 1959. 10. Schaubel, H. J.: Orthopedics 1:274, 1959.